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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pyramax

International non-proprietary name: pyronaridine / artesunate

Procedure No. EMEA/H/W/002319/X/0008/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ACPR	Adequate clinical and parasitological response
ACT	artemisinin-based combination therapy
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AL	artemether/lumefantrine
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	Artesunate
ASAQ	Artesunate/amodiaquine
AST	aspartate aminotransferase
AUC	area under the curve
AUC _{0-∞}	area under the curve from time 0 to infinity
AUC _{0-last}	area under the curve from time 0 to last measurable concentration
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C _{max}	peak plasma or blood concentration
CV	coefficient of variation
DHA	Dihydroartemisinin
DHA-PQP	Dihydroartemisinin/piperaquine
ECG	electrocardiogram
EE	efficacy evaluable
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
MQ	mefloquine
MQ + AS	mefloquine + artesunate
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
<i>P. vivax</i>	<i>Plasmodium vivax</i>
PA	pyronaridine tetraphosphate/artesunate
PCR	polymerase chain reaction
PP	pyronaridine tetraphosphate
PSUR	Periodic Safety Update Report
PQ	primaquine
QT _{cB}	QT using Bazett correction
QT _{cF}	QT using Fridericia correction
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
t _{1/2}	half-life
t _{1/2β}	terminal half-life
t _{max}	time to peak plasma or blood concentration
TBM	"to-be-marketed"
ULN	upper limit of normal
ULRR	upper limit of the reference range
V _{2/F}	volume of distribution in central compartment (pyronaridine population pharmacokinetics) or volume of distribution (AS/DHA population pharmacokinetics)
V _{3/F}	volume of distribution in peripheral compartment (pyronaridine population pharmacokinetics) or in central compartment (AS/DHA population pharmacokinetics)
V _{4/F}	volume of distribution in peripheral compartment (AS/DHA population pharmacokinetics)

1. Background information on the procedure

1.1. Submission of the dossier

The Scientific Opinion Holder (SOH), Shin Poong Pharmaceutical Co. Ltd., submitted to the Agency on 10 October 2014 an extension application to the Article 58 CHMP Scientific Opinion for Pyramax (which corresponds, by analogy, to an extension pursuant to Annex I of the Commission Regulation (EC) 1234/200).

The SOH applied for an extension of the marketing authorisation for a new paediatric formulation, Pyramax 60 mg/20 mg Granules for Oral Suspension (Granules), to support the extension of the target population covered by the authorised therapeutic indication for Pyramax to children weighing 5 kg to 20 kg. The SOH also applied for a variation to reflect the results related to the extension application within the Pyramax 180 mg/60 mg Film-Coated Tablets product information.

Pyramax is exclusively marketed outside the European Union.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Joseph Emmerich Co-Rapporteur: Johann Lodewijk Hillege

- The application was received by the EMA on 10 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 28 January 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 January 2015.
- PRAC assessment overview, adopted by PRAC on 12 February 2015.
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 February 2015.
- On 30 March 2015 a SAG expert meeting took place to address questions raised by the CHMP.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 July 2015.
- The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
 - GMP inspections at 1 finished product manufacturing site in Korea between 20th April and 24th April 2015 and at 1 active substance manufacturing site in Korea between 30th June and 2nd July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 August 2015.
- PRAC RMP Advice and assessment overview, adopted on 10 September 2015.

- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 October 2015.
- During the meeting on 19 November 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Pyramax.

2. Scientific discussion

2.1. Introduction

Pyramax (pyronaridine-artesunate: PA) is an antimalarial agent belonging to the artemisinin-based combination therapies (ACTs) class.

Medicinal product and pharmacotherapeutic action

Pyronaridine inhibits the formation of β -haematin thus, preventing the malarial parasite from neutralizing haem, which is toxic to the parasite. Additionally, by forming a drug-haematin complex pyronaridine inhibits glutathione-dependent degradation of haematin and enhances haematin-induced lysis of red blood cells. Both these actions lead to parasite death.

Several mechanisms of action have been proposed to account for the activity of artemisinins; the generation of free radicals inside the parasite food vacuole and inhibition of the parasite's sarcoplasmic endoplasmic reticulum calcium-ATPase are widely accepted.

Rationale for the proposed change

Malaria is a significant global health challenge affecting mainly young children and pregnant women, with approximately 500 million cases and up to 3 million deaths per year. Infants under 12 months of age constitute a significant proportion of patients in malaria endemic countries. Because deterioration in infants can be rapid and may have fatal consequences, the medical need for use in young children is even greater.

To counter the threat of resistance of *Plasmodium falciparum* to monotherapies and to improve treatment outcome, the WHO recommends that artemisinin-based combination therapies (ACTs) be used as first-line treatment for infants and young children with uncomplicated *P. falciparum* malaria. Careful attention should be paid to accurate dosing and ensuring the administered dose is retained. A number of ACTs are now available and include artesunate-amodiaquine (ASAQ), artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHA-PQP) which have shown to be well tolerated and efficacious in treating uncomplicated *P. falciparum* malaria in patients from endemic countries and are now often first or second line therapies in these countries. The artemisinin derivatives are safe and well tolerated by young children, and so the choice of ACT will be determined largely by the safety and tolerability of the partner drug. With the exceptions of sulfadoxine-pyrimethamine, primaquine and tetracyclines, the WHO specifies that there is no evidence for specific serious toxicity for any of the other currently recommended antimalarial treatments in infancy. However, the currently recommended doses of lumefantrine, piperaquine, sulfadoxine-pyrimethamine and chloroquine achieve substantially lower drug concentrations in young children than older patients. Moreover, for the majority of antimalarials, the lack of an infant formulation necessitates the division of adult tablets, which may lead to inaccurate dosing.

The current regulatory submission presents the safety and efficacy profiles for Pyramax granules. Particular reference is drawn to the body of safety data that includes both the patients who received

Pyramax granules alone, and all patients treated with Pyramax (tabulated separately within the submitted documentation). This approach is informed by results from the relative bioavailability study between tablet and granule formulations (SP-C-017-12). Given that pyronaridine is the component of Pyramax implicated in the key safety issue of raised transaminases, the SOH considers it appropriate to incorporate the overall Pyramax safety data in the evaluation of Pyramax granules.

The key safety issues addressed are:

- (i) overall safety in patients < 20kg,
- (ii) safety of repeat dosing (a significant question for a paediatric population at risk of repeated malaria infections within an endemic region), and
- (iii) the assessment of transaminase rises and risk of hepatotoxicity

Reference is made to the following:

(I) the integrated safety analysis of study SP-C-007-07 and the initial dosing from the sub-study of the ongoing repeat-dose longitudinal study SP-C-013-11 in West Africa.

(II) The safety of repeat dosing with Pyramax has been presented in a for label extension of the tablet formulation (variation II-0002 – submitted in parallel).

(III) Within this submission, an evaluation of transaminase rises is emphasized. Both categorical and shift data are assessed, together with the summary of safety. In addition, narratives describing individual progress of patients treated more than once and experiencing a rise in ALT or AST >1.5 x ULN in any period of treatment are provided as well as summary tables.

Data have also been provided in weight categories for patients receiving granules.

New efficacy data have been provided for those patients who were randomised between Pyramax and artemether-lumefantrine, in sub-study of the ongoing SP-C-013-11 trial in West Africa.

No further data are available on the treatment of patients <20 kg suffering from *P. vivax* malaria. This was originally planned but the relevant study SP-C-011-10 was cancelled following a negative outcome in a feasibility assessment. The remaining study SP-C-018-13 in adults infected with *P. vivax* consists of combination regimen with primaquine, with an objective of radical cure.

The SOH claims that there is no ground for the safety profile of Pyramax to be any different to that observed in patients with *P. vivax* > 20 kg or to patients both <20 kg and ≥ 20 kg with *P. falciparum*.

Proposed indication

The following indication is proposed for Granules formulation:

4.1 Therapeutic indications

Pyramax Granules for oral suspension are indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in children and infants weighing 5 kg to under 20 kg.

Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4).

This variation is requests the use of PYRAMAX to the children weighing 5 kg to 20 kg.

In addition, the SOH also the requested changes pertaining to type II variation (EMA/H/W/002319/II-0002 for PYRAMAX Tablets):

- To add the possibility of re-treatment (repeated treatment course)

- To suppress the restriction of using this medicine in areas of low transmission with evidence of artemisinin resistance.

The Package Leaflet and Labelling were proposed to be updated in accordance.

2.2. Quality aspects

2.2.1. Introduction

The present application is a line extension according to article 58 of regulation (EC) 726/2004, concerning the addition of a new pharmaceutical form and new strength for paediatric use.

The finished product is presented as granules for oral suspension containing 60 mg pyronaridine tetraphosphate and 20 mg artesunate as active substances.

Other ingredients are: mannitol, talc, ethyl cellulose, macrogol 6000, hypromellose 2910, tartrazine (E102), sunset Yellow FCF (E110), and acesulfame potassium

The product is available in sachets consisting of layers of polyester, aluminium and polyethylene/Surlyn as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The finished product contains two active substances, artesunate and pyronaridine tetraphosphate. The information of both active substances has recently been assessed and approved in the procedure for Pyramax tablets and no new information has been submitted within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Pyramax Granules for Oral Suspension are orange coloured granules.

The following aspects were taken into consideration for the definition of the finished product QTPP: environmental and technical considerations (high humidity, high temperature, poor healthcare infrastructure, limited access to clean drinking water, cost of goods requirements), the standards of the WHO and other third party bodies such as Global Fund, IMFM, etc., characteristics of the active substances, preferred route of administration, preferred dosage form, dosage strength, intended population (children), container closure system suitability, stability of the finished product in environmental conditions found in malaria endemic countries, and finished product quality attributes (identification, assay, uniformity of dosage form, degradation products, residual solvents, water content, and microbial limits).

Principles of the Guideline on Pharmaceutical Development of Medicines for Paediatric Use, including acceptability, palatability, risk of choking or aspiration, have been taken into account during product development. The bitter taste of pyronaridine tetraphosphate is masked with ethyl cellulose. Acceptability and palatability were not an issue during the phase II and phase III clinical trials and overall feedback

from healthcare worker was positive. The risk of aspiration is mitigated by the granule particle size distribution; the risk for choking is addressed by administration with a small volume of water.

Since the solubility of artesunate in water is low, the particle size distribution of artesunate was considered to be critical for the dissolution of the finished product. It was also considered to be critical with respect to manufacturing processability. Thus, a control parameter for particle size was required. The control of particle size distribution for the artesunate is the same as that for Pyramax tablet. On the other hand, pyronaridine tetrphosphate is a high soluble compound. Since pyronaridine tetrphosphate is freely soluble in water regardless of pH, particle size distribution is not critical with respect to dissolution rate and no specification for particle size distribution has been proposed.

Compatibility studies of 1:1 mixture of both active substances demonstrated the incompatibility of the two active substances.

Some of the excipients used for the manufacture of the granules, namely mannitol, talc, macrogol, hypromellose, tartrazine (E102) and Sunset yellow (E110), are also included in Pyramax film coated tablets. New excipients are ethylcellulose and acesulfame potassium. For all excipients reference is made to the Ph Eur, except for tartrazine (E102) and sunset yellow (E110) for which in-house specifications have been set. The test methods are based on general or compendial procedures, therefore no validation data are provided. The specifications for colorants tartrazine (E102) and Sunset yellow (E110) are in line with EU Regulation 231/2012. In order to delineate possible interactions between potential formulation excipients and the active substances an excipient compatibility study was performed using binary mixtures of each active substance and excipients. These powder samples were placed in polyethylene bottles, sealed and then stored under accelerated conditions (40°C / 75%RH) for 4 weeks. Samples were analysed and no significant changes were observed. The results were compliant with total impurities for each active substance. Considering the risk for allergic reactions documented for the colorants tartrazine and sunset yellow, the CHMP recommends evaluating alternative colorants for their safety profile and formulation development perspective (compatibility, manufacturability). The company should inform the EMA within 9 months on the action plan for developing a formulation without organic colorants.

As the two active substances were shown to be incompatible, the manufacturing method was developed to minimise contact between the two active substances. In addition, as mentioned above, pyronaridine tetrphosphate has a bitter taste which should be masked to improve patient compliance..

The composition of the granules used in phase II and phase III clinical studies is qualitatively identical to the proposed commercial formulation. The amounts of the colourants (tartrazine and sunset yellow FCF) were reduced in the commercial formulation. The amount of mannitol was increased to maintain the overall weight of the granules. These minor formulation changes have no impact on product performance.

An in-vitro comparison of the phase III formulation and the commercial formulation (stability batches manufactured on commercial site) was made. The dissolution profile of phase III clinical batch (basket method) and stability batches (reciprocating cylinder method) in pH 6.8 medium was evaluated. The dissolution testing was performed using the basket method during clinical development, subsequently, a reciprocating cylinder method was developed and validated for routine use on the commercial product. To demonstrate the similarity between basket method and reciprocating cylinder method, the dissolution profile of a stability batch and a phase III clinical batch which was tested using the basket method were compared. Similarity of the dissolution profiles was demonstrated by f_2 analysis. This result showed that the basket method and reciprocating cylinder method are similar.

The in-vitro dissolution profile of the granules and the tablets was also compared. The test was performed using the selected apparatus for granules (i.e. reciprocating cylinder) using one tablet and one sachet of

granules.. The dissolution profiles between tablets and granules are similar for both artesunate and pyronaridine.

However, the dissolution method does not ensure complete dissolution of artesunate active substance. Based on this the CHMP recommends to develop and validate a discriminating dissolution method for artesunate and to update the dissolution specifications for artesunate accordingly.

A clinical trial was also performed to determine the relative bioavailability of the Pyramax Granules for Oral Suspension and Pyramax tablets.

The development of manufacturing process is well documented and clearly explained. Parameters explored at laboratory scale were confirmed at commercial scale on four batches for the critical manufacturing steps. Optimization of the first critical manufacturing process was performed and verified with one additional commercial batch. All the results are compliant with specifications, which demonstrate the appropriateness of the normal operating ranges (NOR) established for manufacturing process for the main steps studied.

The primary packaging is sachets consisting of layers of polyester, aluminium and polyethylene/Surlyn. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several steps: screening, coating, drying, screening, blending, filling and carton/box packing. The process is considered to be a standard manufacturing process.

Adequate in-process controls have been set for the manufacturing steps. The process has been validated on three full scale commercial batches manufactured at the proposed commercial site.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification of artesunate (colour, HPLC), identification of pyronaridine (UV, HPLC) dissolution artesunate (Ph Eur), dissolution pyronaridine (Ph Eur), uniformity of dosage units (Ph Eur), assay artesunate (HPLC), assay pyronaridine (HPLC), related substances artesunate (HPLC), related substances pyronaridine (HPLC), microbiological attributes (Ph Eur), leak test, residual solvent content (GC) and loss on drying (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three commercial scale batches of finished product stored under long term conditions for 24 months at 30°C / 65% RH and at 30°C / 75% RH and for up to 6 months under accelerated conditions at 40°C / 75% RH according to the ICH guidelines were provided. The selection of 30°C / 75% RH as

additional long term storage conditions is considered appropriate for this dosage form as it is intended to cover markets with hot and humid climates (climatic zone IV) where the product will be used. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, dissolution, artesunate related substances, pyronaridine tetraphosphate related substances, uniformity of dosage units, assay, microbiological examination, leak test, residual solvent and loss on drying.

All results complied with the proposed specifications. Trends observed are slight decreases in dissolution and assay of artesunate; and increases of artesunate impurities, and total artesunate impurities at all tested conditions. Slight changes in assay and impurities pyronaridine were only observed at accelerated conditions. Loss on drying tested at release is smaller than tested after storage.

Considering that the product is intended for climatic zones IVb, results under accelerated conditions are within specifications.

Based on available stability data, the shelf-life of 2 years and not store above 30°C as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues pertaining to the dissolution method for artesunate and the colorants included in the formulation which should be resolved *as per* the recommendations stated in 2.2.6. These points are considered acceptable by the CHMP.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the SOH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To develop and validate a discriminating dissolution method for artesunate and to update the dissolution specifications for artesunate accordingly.

- To explore the possibility and to present an action plan for developing a formula containing inorganic colorants, without risk for allergic reactions. The company should inform the EMA within 9 months on the action plan for developing a formulation without organic colorants.

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data have been submitted.

In the initial Pyramax submission, the SOH stated that studies in juvenile animals were ongoing to support future submissions for treatment of children of < 15 Kg. These data were nevertheless not provided in this application. The SOH justified the absence of these studies (see discussion).

In the extension of indication application II-0002, submitted in parallel, the SOH discussed the underlying mechanism of hepatotoxicity for pyronaridine. Submitted study reports showed:

1. Study to explore the potential for pyronaridine to impair mitochondrial function (A Borgne-Sanchez)

Pyronaridine induces mitochondrial alterations in isolated mouse liver mitochondria and more strongly in human cultured hepatocytes. Consequently, hepatotoxicity of Pyronaridine which occurs in a small proportion of treated subjects during clinical trials could be attributed to mitochondrial toxicity.

2. Cytotoxicity of pyronaridine in primary hepatocytes (Xiaoli Meng)

This study concluded that Pyronaridine had a potent cytotoxic effect on primary hepatocytes (rat and human), and the cytotoxicity is dependent on the intracellular glutathione level or the glutathione redox cycle and may be caused by oxidative damage. Consequently, Quinone reductase, transporter, or glutathione reductase may play an important role in the detoxifying process.

2.3.2. Ecotoxicity/environmental risk assessment

An environmental risk assessment has not been submitted with this application.

2.3.3. Discussion on non-clinical aspects

As part of the line extension application, a widening of the indication for Pyramax is applied for, to include children and infants weighing from 5 to 20 Kg. No juvenile toxicity study has been conducted with pyronaridine or artesunate. The SOH justifies this absence due to clinical data available in paediatric patients, superseding this requirement:

- Concerning artesunate, the need for juvenile animal study has been superseded by clinical experience with the combination as artemisinin derivatives are already approved for use in young children and considered well tolerated in this age group at a similar dose.

- Concerning pyronaridine, it is noted that non-clinical data have some limitations to characterize the level of risk in juvenile animals in comparison to adult animals in view of the low exposure of pregnant rats and pups in the peri/ post-natal study, the long terminal half-life (2-4 days in rat and 2.5 days in dog), the accumulation of pyronaridine observed in toxicology studies in rats and dogs in many organs/tissues that are developing in the intended age group and the non-fully reversible toxicity in adult animals without an appropriate safety. However, taking account of clinical experience obtained in 2180 patients aged < 18

years and specifically 667 patients targeted by the granules formulation, it is accepted by CHMP that the further conduct of juvenile toxicity studies would be of limited relevance.

Based on the non-clinical investigation, knowledge has been gained on the mechanistic aspects of the toxicity. This seems a dose dependent mechanism which involves, as for paracetamol, the formation of a hepatotoxic reactive metabolite which could be detoxified by glutathion (GSH).

2.3.4. Conclusion on the non-clinical aspects

No juvenile toxicity study has been conducted with pyronaridine or artesunate. However, reassurance on the use of this ACT in young children has been derived, based on clinical data obtained in the paediatric population.

Knowledge has been gained on the mechanistic aspects of the toxicity, which seems to involve the formation of a hepatotoxic reactive metabolite which could be detoxified by glutathion (GSH).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the European Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The main data submitted by the SOH are as follows:

- **Study SP-C-017-12** : a relative bioavailability study between tablet and granule formulations

"Phase I, open-label, cross-over study to investigate the relative bioavailability of Pyramax (pyronaridine-artesunate) in tablet and granule formulations, in healthy volunteers."

- **Study SP-C-013-11**

"WANECAM (SP-C-013-11) study: A Phase IIIb/IV Comparative, Randomised, Multi-centre, Open Label, Parallel 3-arm Clinical Study to Assess the Safety and Efficacy of Repeated Administration of Pyronaridine-artesunate, Dihydroartemisinin-piperaquine or Artemether-lumefantrine or Artesunate-amodiaquine over a 2-year Period in Children and Adult Patients with Acute Uncomplicated Plasmodium sp. Malaria."

This longitudinal study (SP-C-013-11) has been undertaken in three West African countries which allowed Pyramax to be tested over a number of malaria seasons in patients presenting with uncomplicated malaria. This longitudinal study involves the two new ACTs, Pyramax and DHA- piperaquine (DHA-PQ), compared to the local first line ACT therapies, being either ASAQ or AL depending on the site. The study examined safety and efficacy of these ACTs given for consecutive malaria episodes over a two year follow-up period.

Two sub-study analyses and clinical sub-study reports have been prepared. The sub-study population comprises all patients treated with PA or AL for efficacy and all PA patients for safety, in the period from the start of the study (October 2011) to the last enrolment on or by 31 October 2013 (with the last

follow-up visit, for the purposes of this sub-study analysis, on 12 December 2013). The enrolment was completed in December 2013 and the last patient's last visit is to occur in January 2016.

The first sub-study forms the basis of a submission to the European Medicinal Agency to amend the Summary of Product Characteristics (SmPC) regarding repeat administration of Pyramax tablets for the treatment of recurrent malaria episodes (variation II/02).

The second sub-study forms the basis of a line extension to amend the Summary of Product Characteristics (SmPC) to include the paediatric formulation of Pyramax granules for oral suspension for repeat administration of the treatment of recurrent malaria episodes.

- **Study SP-C-007-07 :**

"A Phase III Comparative, Open-Labelled, Randomised, Multi Centre Clinical Study to Assess Safety and Efficacy of a Fixed Dose of Oral Pyronaridine/Artesunate (PA) Granule Formulation (60:20 mg) (Paediatric PYRAMAX®) Versus Coartem® (Artemether/Lumefantrine) (AL) Crushed Tablets in Infants and Children With Acute Uncomplicated Plasmodium falciparum Malaria."

This study has previously been addressed and is referred to in the EPAR pertaining the initial scientific opinion.

Safety data analysis of patients from study SP-C-007-07 has been pooled with safety data from SP-C-013-11.

2.4.2. Pharmacokinetics

In the context of pediatric extension, the SOH developed a 60 mg/20 mg Granules for Oral Suspension (Granules) and seeks the use of Pyramax combination in younger children weighing 5 to 20 kg. Taking into account the nature of the application, it is expected that the biopharmaceutical performances of the new formulation be tested and compared to the already approved drug product. Also, the PKs in the new target population at the claimed dose should be characterized in order to support the efficient and safe use of the drug.

Besides, the data package already provided by the SOH and assessed in the initial submission, the additional documentation consists of:

- comparative bioavailability (tablet versus oral suspension) study performed in healthy adult subjects (Study SP-C-017-12)
- Focus on pediatric data from Phase 2 study (SP-C-003-05): in this study maximum DHA concentrations and overall DHA exposure were investigated after the administration of PA (Pyronaridine/Artesunate) granules or tablets in uncomplicated malaria-infected patients.
- Focus on pediatric data from Phase 3 pediatric clinical trial (SP-C-007-07) in malaria patients. Blood samples were collected and assayed for DHA concentrations. The obtained concentrations were compared to the DHA concentrations from pediatric patients administered the tablet formulation in other PA clinical trials.

Study No. SP-C-017-12

A phase I, open-label, cross-over study to investigate the relative bioavailability of Pyramax [Pyramax (pyronaridine-artesunate)] in tablet and granule formulations, in healthy volunteers.

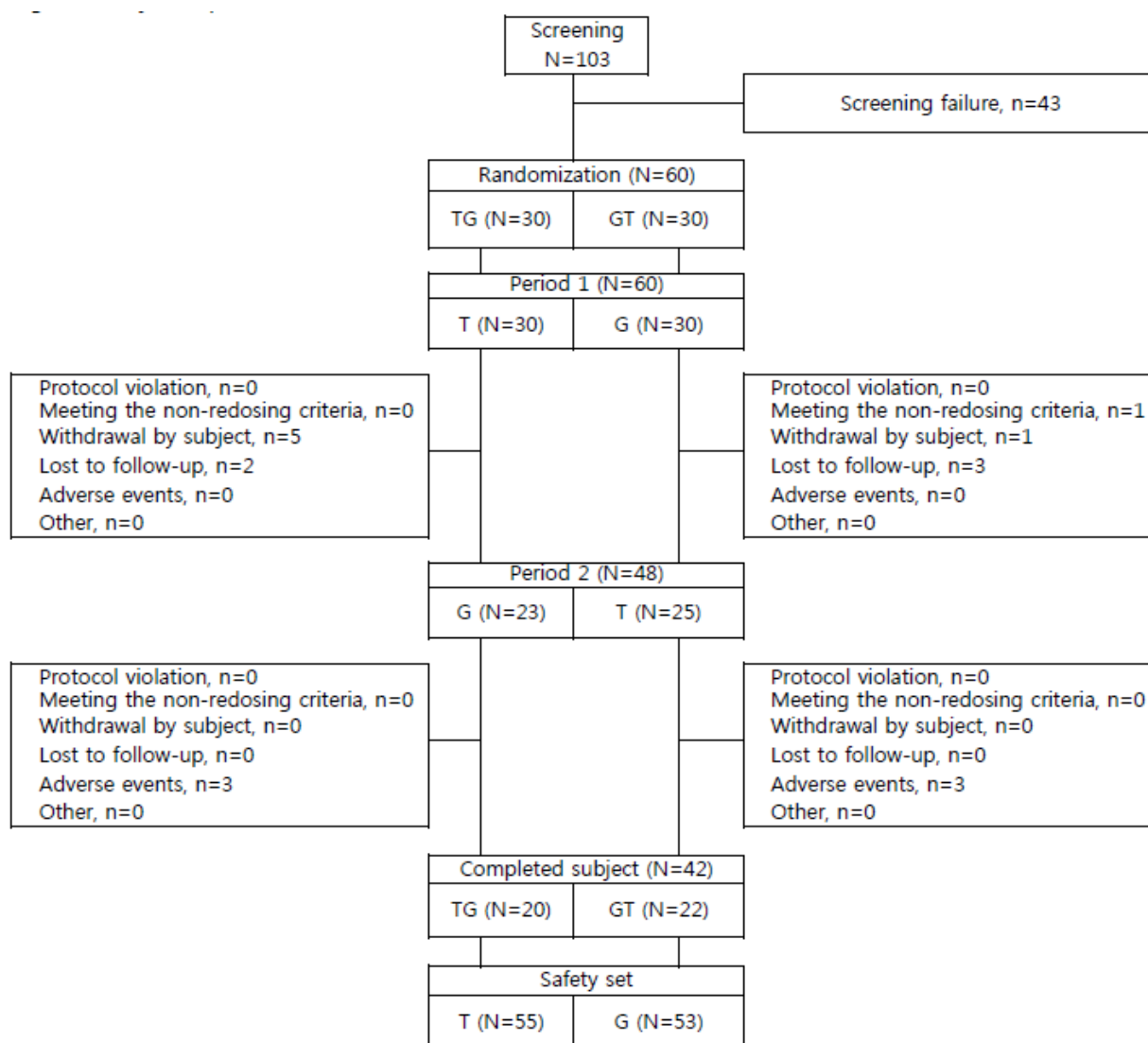
Methods

Study design

The primary objective of this study was to assess the relative bioavailability of the fixed dose combination of Pyramax (PA; pyronaridine-artesunate [3:1]) in tablet and granule formulations in healthy adults.

This was a Phase I, single centre open-label, randomized, two-way cross-over study in healthy volunteers to compare the bioavailability of two formulations of PA, in tablet and in granule formulation. A single dose of each of the two formulations was administered to all volunteers according to the assigned sequence, separated by a 60-day wash-out period. The study duration from the first study drug administration (Day 1) through to the last follow-up, was approximately 103 days. Screening was to be performed within 28 days before Day 1. Two single doses, separated by a wash-out period of 60 days

PK parameters of DHA rather than artesunate were jointly considered with the PK parameters of pyronaridine as the primary bioavailability metrics and thus used for the sample size calculation. Sample size calculations used the two one-sided t tests approach with generation of 90% CI for the test/reference geometric mean ratio and were generated using nQuery Advisor.



T: Tablets, G: Granules

Analytical methods:

- Pyronaridine levels were measured in whole blood using a validated LC-MS technique. This technique has been already used in the PK development program. Data regarding validation and QC has been reported and assessed in the initial submission.
- Artesunate and DHA: Plasma levels of both analytes were measured using validated LC-MS technique. This technique has been already used in the PK development program. Data regarding validation and QC has been reported and assessed in the initial submission.

PK Analysis:

The primary pharmacokinetic (PK) outcome measure was the area under the concentration-time curve from Hour 0 to the last sampling point (AUC0-t) for pyronaridine and dihydroartemisinin (DHA).

Secondary PK outcome measures included:

- Pyronaridine: area under the concentration-time curve from Hour 0 to infinity (AUC0-inf), area under the concentration-time curve from Hour 0 to 72 hours post-dose (AUC0-72), maximum peak observed concentration (Cmax), time to achieve maximum peak observed concentration (Tmax), and terminal half-life.
- Artesunate: AUC0-t, AUC0-inf, Cmax, Tmax, and terminal half-life.
- DHA: AUC0-inf, Cmax, Tmax, and terminal half-life.

Statistical Methods:

The relative bioavailability of artesunate, DHA, and pyronaridine after administration as either granules (test formulation) or tablets (reference formulation) was compared as follows:

The geometric mean of the ratios of the formulations (test/reference) was reported as a point estimate with a 90% confidence interval (CI) for each of the following: AUC0-t, AUC0-inf, and Cmax of artesunate, DHA, and pyronaridine, and AUC0-72 of pyronaridine.

The granule formulation of PA was considered the test treatment and the marketed tablet formulation of PA was considered the reference treatment.

The primary outcome of interest was the effect of the PA formulation on pyronaridine and DHA AUC0-t values. Relative bioavailability of the granule (test) and the tablet (reference) formulations were investigated by comparing the 90% CI for pyronaridine and DHA AUC0-t values to the no relevant difference interval of 80% to 125%.

Results

The outcome of the study is summarized below respectively for the three tested entities: Pyronaridine (Figure 1 and Table 1), Artesunate (Figure 2 and Table 2) and DHA (Figure 3 and Table 3):

Figure 1 Plot (linear scale) of Mean Pyronaridine Concentration versus Time up to 72 Hours Post-dose (Volunteers who completed both Periods)

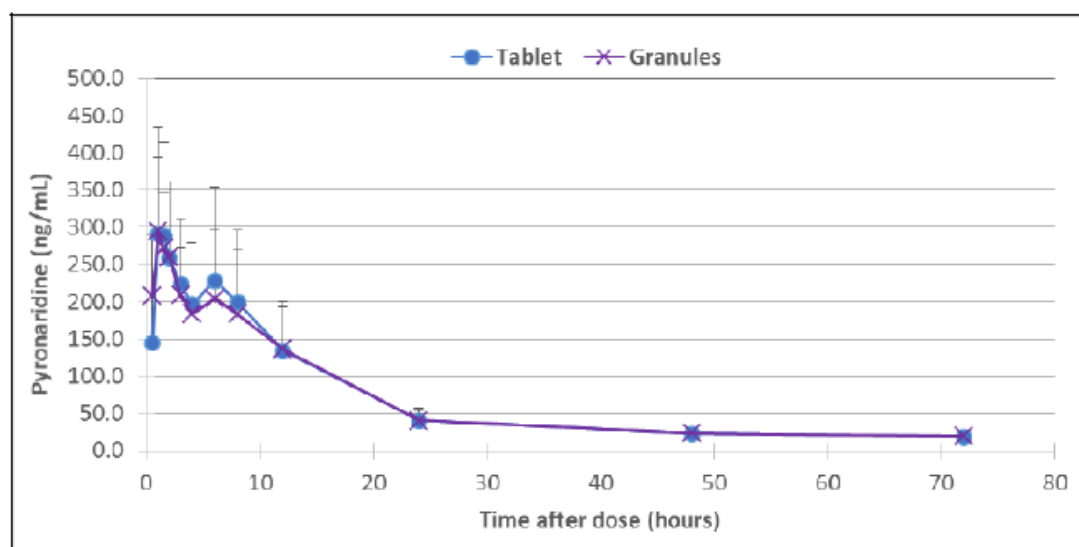
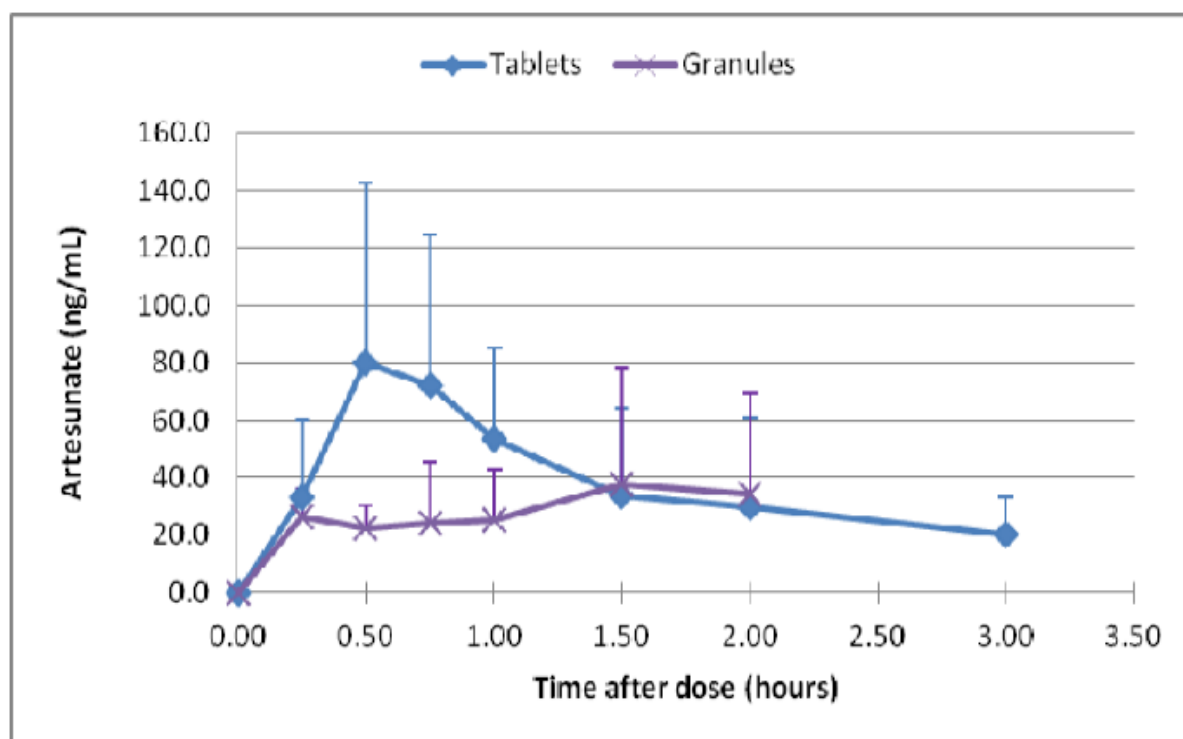


Table 1: Pyronaridine pharmacokinetic parameter estimates and 90% confidence intervals for the ratios (granules/tablets) of geometric means:

	Geometric Mean (CV %)		Test/Reference Point Estimate (%)	Test/Reference 90% CI (%)	N Sample size
	Test (oral suspension)	Reference (Tablet)			
AUC inf (ng*mL/h)	17431 (38.38)	17064 (34.8)	98.8	[91.7; 106.4]	N=26
AUC	4315 (34)	4348 (39.6)	100.1	[94.43;106.12]	N=42
Cmax (ng/mL)	390.5 (32.4)	315.5 (50)	98.74	[90; 108.3]	N=42
Tmax (h)	1.3 (125.9)	1.6 (130)	NS	NA	N=42

Figure 2 Plot (linear scale) of Mean Artesunate Concentration versus Time afterDose (Volunteers who Completed both Periods):



Only time points with at least 50% of concentrations above LLOQ for a given formulation are plotted.
Error bars represent 1 standard deviation.

Table 2: Artesunate pharmacokinetic parameter estimates and 90% confidence intervals for the ratios (granules/tablets) of geometric means:

	Geometric Mean (CV %)		Test/Reference Point Estimate (%)	Test/Reference 90% CI (%)	N Sample size
	Test (oral suspension)	Reference (Tablet)			
AUC inf (ng*mL/h)	112 (68.7)	106 (38.6)	105.5	[77.11; 144.39]	N=6
AUCt (ng*mL/h)	74 (52.3)	85 (55.4)	86.55	[77.87; 96.21]	N=42
Cmax (ng/mL)	48.6 (63)	90 (67.2)	53.77	[46.43; 62.27]	N=42
Tmax (h)	1.22 (87.4)	0.86 (54.3)	NS	NA	N=42

Figure 3 Plot (linear scale) of Mean DHA Concentration versus Time after Dose (Volunteers who completed both Periods):

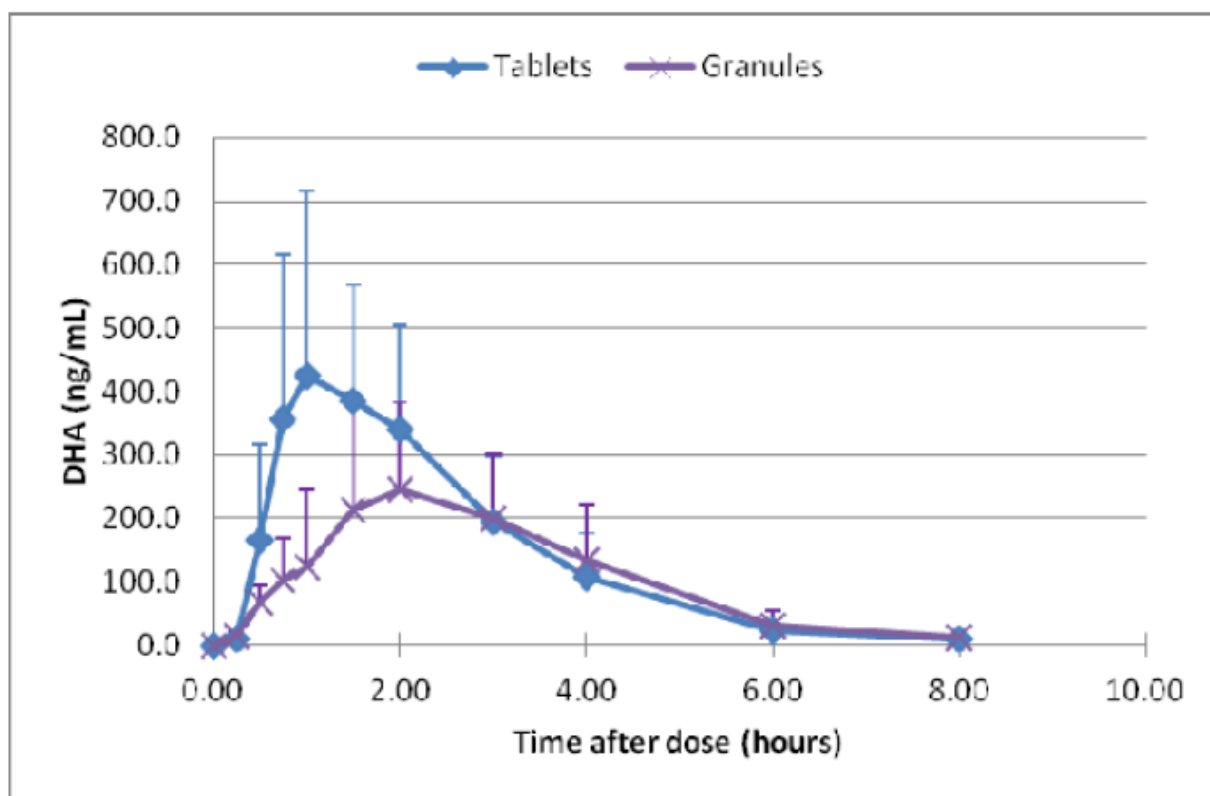


Table 3: DHA pharmacokinetic parameter estimates and 90% confidence intervals for the ratios (granules/tablets) of geometric means:

	Geometric Mean (CV %)		Test/Reference Point Estimate (%)	Test/Reference 90% CI (%)	N Sample size
	Test (oral suspension)	Reference (Tablet)			
AUC inf (ng*mL/h)	791 (39.3)	1092 (32)	72.35	[67.43; 77.63]	N=41
AUCt(ng*mL/h)	771 (39.6)	1064 (33.2)	72.49	[67.56; 77.78]	N=42
Cmax (ng/mL)	297.4 (42.7)	517.4 (46.4)	57.26	[50.48; 64.96]	N=42
Tmax (h)	2.11 (38.7)	1.32 (46.8)	NS	NA	N=42

- The pyronaridine results support a lack of any clinically relevant formulation-related difference in pyronaridine exposure.
- Peak concentrations of both artesunate and DHA were lower following administration of the granule, as compared to the tablet formulation.
- Artesunate and DHA AUC_{0-t} values also averaged lower with the granule formulation.

Special populations

PK characterisation in paediatric patients

Plasma and blood samples were collected in uncomplicated malaria infants were collected in Phase 2 (SP-C-003-05) and Phase 3 (SP-C-007-07) studies in order to characterize the PKs of the drug in the target population.

Phase 2 Study SP-C-003-05

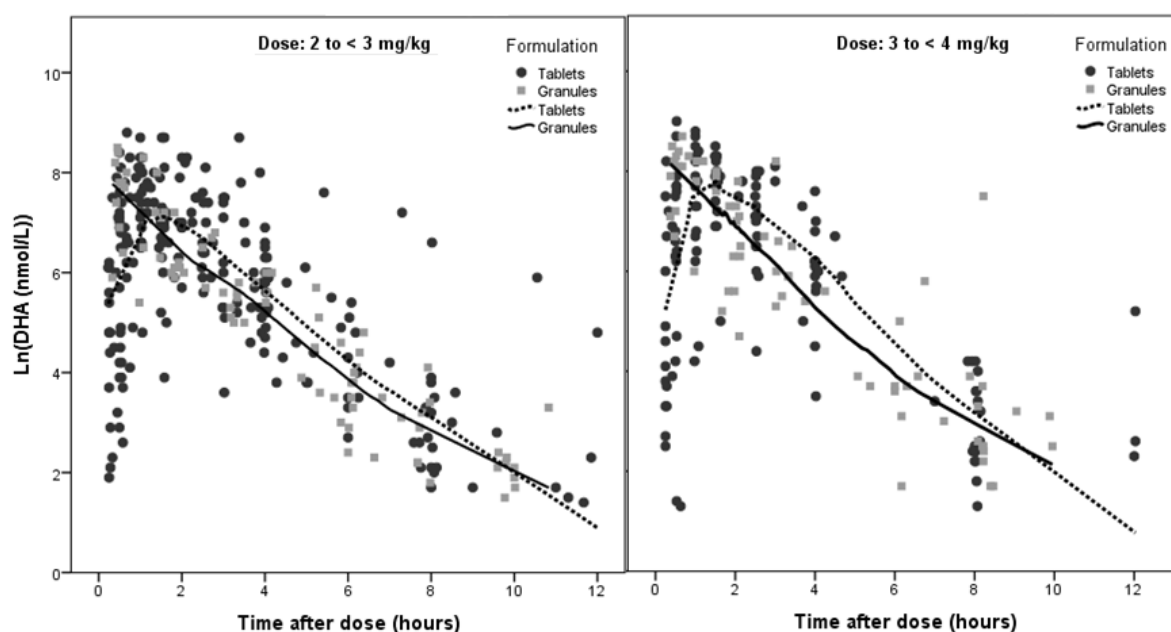
Study SP-C-003-05 was part of the initial submission documentation and included children aged 2 to 14 years and weighing 10 to 40 kg. No children under 2 years or weighing less than 10 kg were included in the study. From this study it was concluded that the pharmacokinetics of artesunate in children with falciparum malaria is similar to healthy adults in terms of $t_{1/2}$ and bioavailability. The pharmacokinetic results in this study were similar for DHA compared with literature reports on children with *P. falciparum* malaria. The pyronaridine $t_{1/2}$ was similar to that in healthy adult volunteers in Phase I. Also it was concluded from this study that similar systemic exposure is observed with the tablets and granules when both formulations are administered at the same molar dose.

Phase 3 Study SP-C-007-07

In Study SP-C-007-07 sparse data were collected in children aged 0.6 to 10 years and weighing 9 to 24.3 kg. However, the data collected in children under 2 years seems very limited and no data are available in children under 7 months or weighing less 9 kg.

Additionally, DHA concentrations obtained from that trial are also plotted (Figure 4) along with concentrations from paediatric patients administered the tablet formulation in other PA clinical trials. As is apparent from this figure, patients administered similar mg/kg doses in the granule and tablet formulation displayed similar DHA concentrations, indicating that the granule and tablet formulations are associated with reasonably equivalent DHA exposure in paediatric malaria patients.

Figure 4: Plots, Stratified by Dose, of DHA Concentrations Observed in Paediatric Malaria Patients in Phase 3 PA Trials:



The data collected in both studies (SP-C-003-05 and SP-C-007-07) were part of the dataset analysed using population analysis.

2.4.3. Pharmacodynamics

No new data were submitted.

2.4.4. Discussion on clinical pharmacology

Based on the submitted bioequivalence study the granule and tablet pyronaridine/artesunate formulations are considered bioequivalent with respect to pyronaridine. However, with respect to artesunate, lower artesunate C_{max} (-13%) and AUC levels (-46%) are observed after administration of the granules compared to the tablets. This is also the case for its active metabolite dihydroartemisinin (DHA) showing a 43 and 28% lower C_{max} and AUC value, after administration of the granules.

A possible reason for the lower artesunate concentrations after administration as granules may be that dissolution is faster as can be observed in the t_{max} values between the granules and tablets (1h vs. 1.5h). As concluded by the applicant, artesunate is neutral at gastric pH, and, as in this bioequivalence study, blood concentrations of artesunate are always detected early, typically by 15 minutes post-dose, suggesting that gastric absorption of artesunate is a contributing factor to overall absorption.

Artesunate displays a somewhat limited solubility in water. At pH 7, solubility is 0.296 mg/ml. Solubility decreases with decreasing pH, with solubility at pH 1 of less than 0.2 mg/ml. Furthermore, artesunate also displays rapid acid-catalyzed hydrolysis to its active metabolite, DHA, at gastric pH levels. The half-life for such hydrolysis at pH values of 1.2 is estimated to be 26 minutes. Therefore, were one formulation associated with more rapid dissolution of artesunate, a greater number of artesunate molecules would be subject, at any given time, to the competing processes of absorption and hydrolysis. Given the rapidity of the acid-catalyzed hydrolysis reaction, it may be likely that the net effect of such an enhanced dissolution rate would be an increase in artesunate to DHA hydrolysis rather than increase in artesunate absorption.

Based on this mechanism, it follows that a greater proportion of the pool of artesunate + DHA entering the intestine will be in the form of DHA for the granule, as compared to the tablet formulation. In healthy volunteers, DHA may display poor bioavailability relative to artesunate (Haynes RK et al., Artesunate and dihydroartemisinin (DHA): unusual decomposition products formed under mild conditions and comments on the fitness of DHA as an antimalarial drug. Chem Med Chem. 2007; 2: 1448-1463), therefore, the greater proportion of DHA entering the intestine following administration of the granule formulation would be expected to result in lower exposure to DHA, as compared to the tablet formulation, as was observed in this study.

The SOH indicated that the lower artesunate and DHA concentrations observed in this study in healthy volunteers may be applicable to malaria patients, as the later may have increased gastric pH. As such, a slower conversion would be expected in malaria patients.

In the Phase II study SP-C-003-05, including paediatric subjects with uncomplicated *P. falciparum* malaria, subjects were included from 2 – 14 years old, with a body weight between 10 and 40 kg. The subjects received the combination of pyronaridine and artesunate in a 3:1 ratio. Next to the tablet formulation, the subjects received also a granule formulation. As this was not a crossover study and a high variability was observed, it cannot be excluded that the granule formulation and tablet formulation were not bioequivalent.

In addition, the current granule formulation was also used in a Phase III paediatric clinical trial (SP-C-007-07) in malaria patients. DHA concentrations obtained from that trial plotted versus concentrations from paediatric patients administered the tablet formulation in other PA clinical trials (see figure PK 4), did not indicate a large difference, as patients administered similar mg/kg doses in the granule and tablet formulation displayed similar DHA concentrations, indicating that the granule and tablet formulations are associated with reasonably equivalent DHA exposure in paediatric malaria patients. As this was also not a crossover study and a high variability was observed, it cannot be excluded that the granule formulation and tablet formulation were not bioequivalent. However both studies indicate that in patients, the difference observed in the bioequivalence study for DHA in healthy volunteers may be not that pronounced.

Pyramax PKs in children under two years or weighing less than 10 kg is poorly characterized. Phase 2 study SP-C-003-05 investigated only children over 2 years and weighing more than 10 kg. Few data were collected in children aged 0.6 to 2 years and no data were collected in children weighing less 9 kg in phase-3 study (SP-C-007-07).

The recommendation of use (dosing scheme) in children weighing less than 20 kg and more than 8-10 kg was overall judged to be empirical. In order to support the claimed dosing scheme in this group of patients, the systemic exposure obtained with the claimed dosing scheme was simulated (predicted) using the already developed population-PK model and compared to adult patients. The model was refined by inclusion of data from study SP-C-007-07 and SP-C-013-11 in the dataset and formulation as covariate in the model. Simulations suggest that the chosen dosing regimen could be viewed as appropriate.

2.4.5. Conclusions on clinical pharmacology

No definite conclusion on the bioequivalence of PA granules for oral suspension to PA tablets can be made as no specific bioequivalent study in malaria patients has been conducted. PopPK data on artesunate exposure in malaria infected patients suggests that exposure of artesunate is similar to exposure from the tablets. Taking the above into account, the recommendation of use and the claimed dosing scheme of the granule formulation in paediatric population has to be judged in view of the adequacy of the provided clinical data on safety and efficacy.

2.5. Clinical efficacy

2.5.1. Dose response studies

No specific dose response study has been performed in children <20 kg. The adequacy of the dosing regimen is to be judged on the basis of the two main studies SP-C-007-07 and SP-C-013-011.

2.5.2. Main studies

Study n° SP-C-007-07

A Phase III Comparative, Open-Labelled, Randomised, Multi-Centre Clinical Study to Assess Safety and Efficacy of a Fixed Dose of Oral Pyronaridine/Artesunate Granule Formulation (60:20 mg) (Paediatric PYRAMAX®) Versus Coartem® (Artemether/Lumefantrine) Crushed Tablets in Infants and Children With Acute Uncomplicated Plasmodium falciparum Malaria.

Methods

Multi-centre, randomised, comparative, parallel-group, open-label, non-inferiority phase III study of the efficacy and safety of a 3-day regimen of the fixed combination of pyronaridine/artesunate (3:1) versus artemether/lumefantrine in subjects ≤ 12 years of age with acute uncomplicated *Plasmodium falciparum* mono-infection. Subjects were followed for safety for 42 days after the first dose of study drug. The primary efficacy end point was at Day 28.

This clinical trial conducted at 7 sites (East, Central and West Africa and in Philippines).

Study Participants

Paediatric patients (≤ 12 years of age) suffering from acute, symptomatic, uncomplicated *P. falciparum* malaria were recruited from 7 investigative sites in Burkina Faso, the Democratic Republic of Congo, Gabon, The Ivory Coast, Kenya, Mali, and The Philippines.

Patients were eligible to participate if they:

- o Were male or female, ≤ 12 years of age with a body weight ≥ 5 kg and < 25 kg, with no clinical evidence of severe malnutrition, defined as a child whose weight-for-height is below -3 standard deviations or $< 70\%$ of the median of the National Centre for Health Statistics/ WHO normalised reference values.
- o Had acute uncomplicated *P. falciparum* mono-infection defined by:
 - o presence of fever (axillary temperature $\geq 37.5^{\circ}\text{C}$ or oral/tympanic/rectal temperature $\geq 38^{\circ}\text{C}$) **or** documented history of fever in the previous 24 hours **and**
 - o positive microscopy of *P. falciparum* with parasite density between 1,000 and 100,000 asexual parasite count/ μl blood
 - o Were able to swallow oral medication, and able and willing to participate (the patient was to comply with all scheduled follow-up visits until day 42).
 - o Written informed consent was obtained for each patient (if subject was unable to write, according to local ethical considerations witness consent was permitted)

Treatments

Subjects were randomised to receive either oral PA granule formulation (60:20-mg granules sachets) once a day for 3 consecutive days (Days 0, 1, and 2) or AL (20:120-mg crushed tablets) twice a day for 3 consecutive days (Days 0, 1, and 2).

Subject weight recorded during the physical examination at screening was used to calculate the number of sachets/tablets to be administered per dose on all study days.

Subjects randomised to paediatric PA received between 1 and 3 sachets a day based on body weight as follows: ≥ 5 - < 9 kg, 1 sachet; 9- < 17 kg, 2 sachets; 17- < 25 kg, 3 sachets. For subjects randomised to receive PA, dosing on the 2 subsequent days occurred no less than 10 hours after the previous dosing.

Subjects randomised to AL received 1 or 2 crushed tablets (each tablet contained 20 mg artemether and 120 mg lumefantrine) twice a day based on body weight as follows: ≥ 5 - < 15 kg, 1 tablet; 15- < 25 kg, 2 tablets. Subjects randomised to receive AL crushed tablets received 2 administrations per day for each of the 3 treatment days. The Day 0 second dose occurred 8 hours after the first dose. The first dose on Day 1 occurred 24 hours after the Day 0 first dose. Dosing then occurred every 12 hours after the previous dosing for the last 3 doses (6 doses in total).

The PA and AL oral suspensions were prepared immediately before each administration. Water for dispersion and consumption following dosage administration must not have been carbonated.

Study drugs were given to each subject by the Third Party Investigator, with up to 150 mL (full glass) of liquid. Subjects were to take the medication in an upright position (seated or standing).

The qualitative and quantitative composition of the granule significantly differs from tablets.

Based on the available data, no bioequivalence can be established between the two formulations.

Objectives

The primary objective of this clinical study was to demonstrate the efficacy of a fixed combination of PA granule formulation (60:20 mg) by showing a PCR-corrected adequate clinical and parasitological cure rate of more than 90%.

Secondary objectives of this clinical study were to compare the efficacy (non-inferiority) and safety of PA granule formulation compared to Coartem (artemether/lumefantrine [AL]) crushed tablets in a paediatric population and to assess the safety of PA granule formulation.

Outcomes/endpoints

The primary efficacy end point for the study was the proportion of subjects with PCR-corrected ACPR on Day 28. The ACPR was based on the clearance of asexual parasitaemia without recrudescence within x days of initiation of study treatment (where x=particular study day), and not meeting other criteria of early treatment failure, late clinical failure, and late parasitological failure.

Secondary endpoints were:

- Proportion of subjects with PCR-corrected ACPR on Day 14
- Crude ACPR (non-PCR corrected ACPR) on Day 14 and Day 28
- Parasite Clearance Time (PCT)
- Fever Clearance Time (FCT)
- Proportion of subjects with cleared parasites at Days 1, 2, and 3
- Proportion of subjects with fever cleared at Days 1, 2, and 3

Sample size

For the primary objective, a total of 320 evaluable subjects in the PA group would provide 91% power to reject the null hypothesis H_0 : cure rate at Day 28 is $\leq 90\%$ in favor of the alternative H_1 : cure rate $> 90\%$ (assuming an expected cure rate of 95%) using a 1-sided exact binomial test with a nominal significance level of 2.5%.

For the secondary objective: Assuming a cure rate on Day 28 of 95% in both treatment groups and assuming a non-inferiority limit of -10%, then a sample size of 480 evaluable subjects randomised in 2:1 ratio (320 subjects to PA and 160 to AL) would provide $> 99\%$ power to demonstrate non-inferiority of PA compared to AL crushed tablets, using a 2-sided 95% confidence interval with normal approximation.

Assuming a dropout rate of 10%, a total of 534 subjects were to be enrolled in the study (356 subjects to PA and 178 to AL).

Randomisation

Subjects who met all entry criteria and no exclusion criteria were randomised in a 2:1 ratio to receive either PA granule formulation in sachet or AL crushed tablets according to the randomisation scheme

provided by the sponsor. Subjects were assigned a randomisation number in ascending order and were allocated an individually numbered treatment pack. The study was randomised, with a maximum of 150 subjects to be included per site.

Blinding (masking)

This study was open-label. However, the secondary packaging of the study medication was blinded in order to ensure a proper randomisation with no bias. Blinded subject pack labels included study number, drug names, randomisation number, batch number, expiration date, storage information, sponsor's name, and the information that the product was to be administered by study staff after randomisation only and only to be used for clinical study purposes. The sponsor remained blinded throughout the conduct of the trial. No code breaks were required during the course of the study.

Statistical methods

The EE analysis was considered the primary efficacy analysis. The primary efficacy analysis was repeated for the ITT population.

The secondary efficacy analysis tested the non-inferiority of PA compared to the AL group with regard to the PCR-corrected ACPR response rate on Day 28 using a 2-sided 95% confidence interval (Newcombe Wilson score method without continuity correction) and a 10% non-inferiority margin for the EE population. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval for the difference in 28-day PCR-corrected ACPR was not lower than -10%.

If non-inferiority of PA was demonstrated, the p-value associated with a superiority test was calculated based on a 2-sided Chi-Square test (assuming the estimated difference in response rates was in favour of the PA group). If the calculated p-value was <0.05, then the superiority of PA over AL was statistically demonstrated. No multiplicity testing adjustment was required as this testing procedure corresponds to a closed test procedure.

The same statistical analysis was repeated for the 14-day PCR corrected ACPR and the crude 14-day and 28-day ACPR. It should be noted that subjects who discontinued from the study prior to Day 14 were excluded from the EE analysis.

The PCT and FCT were summarised using Kaplan-Meier estimates. Treatment group comparison of PCT and FCT was done by means of the log-rank test. Subjects who did not have (confirmed) parasite or fever clearance within 72 hours after the first dose of study drug were censored at that time point. The proportion of subjects with parasite clearance/fever clearance on Day 1 (24 hours after first dose), Day 2 (48 hours after first dose), and Day 3 (72 hours after first dose) was calculated using Kaplan-Meier estimates. The associated 2-sided 95% CI was also calculated.

Results

Participant flow

Table 4	PA n%	AL n%	Total n%
Subjects randomised	355	180	535
Subjects randomised but not treated	0	0	0
Subjects treated ^a	355 (100.0)	180 (100.0)	535 (100.0)
Subjects who completed treatment ^b	349 (98.3)	174 (96.7)	523 (97.8)

Subjects who completed study	274 (77.2)	142 (78.9)	416 (77.8)
Subjects who discontinued	81 (22.8)	38 (21.1)	119 (22.2)
Adverse event/SAE	6 (1.7)	3 (1.7)	9 (1.7)
Consent withdrawn	2 (0.6)	2 (1.1)	4 (0.7)
Lost to follow-up	6 (1.7)	1 (0.6)	7 (1.3)
Other (parasite re-appearance/malaria)	67 (18.9)	32 (17.8)	99 (18.5)
<i>Note: Percentages are based on the number of randomised subjects.</i>			
<i>a. Received ≥ 1 dose of study medication.</i>			
<i>b. Received all 3 (PA group)/6 (AL group) planned doses of study medication.</i>			

A total of 535 patients were randomised aged less than 12 years were randomised in a 2:1 ratio (n= 355 to the PA group and n= 180 subjects to the AL group) to receive for 3 consecutive days in an open label design oral pyronaridine/artesunate (PA) (60mg:20 mg granules) once daily (full 3 dose treatment : PP: 21.6 to 40 mg/kg; AS: 7.52 to 13.5 mg/kg) or oral artemether/lumefantrine (AL) (Coartem 20:120 mg crushed tablets), twice a day (full 6-doses treatment from 8.4 to 24 mg/kg for artemether and from 51.6 to 144 mg/kg for lumefantrine).

The majority of subjects completed the 3 days treatment: 97.8% = 523/535 (PA group: 98.3% = 349/355; AL group: 96.7% = 174/180) and 77.8% (416/535) completed the study (PA group: 77.2% (274/355); AL: 78.9 % (142/180)).

In the 6 PA and 6 AL patients who did not complete the treatment, 2 PA patients (and none in the AL group) were to be considered as early treatment failures. The description provided by the SOH does not specify the age of those patients. Unfortunately without susceptibility data and assessment of plasma levels at the time of withdrawal, it cannot be established whether those failures would have been related to strain resistance to both active drugs or to sub-therapeutic plasma levels.

Overall, a rate of 22.2% patients discontinued the study with a similar frequency in each group: PA: 22.8%, AL 21.1%. Parasite re-appearance/malaria was the most common reason reported for withdrawal from the study (18.5%).

Recruitment

The study report states that first patient enrolled on 19 November 2007 and last patient completed on 15 September 2008.

Conduct of the study

There were no amendments to the original protocol (28 June 2007). There was 1 amendment to the original SAP (20 February 2009) that occurred after database lock.

Baseline data

The majority were black (96.1%) subjects and from Africa: 96.3% (515/535): 5.2% were recruited in Burkina Faso (Ouagadougou), 15.7% at a site in Democratic Republic of Congo (Kinshasa), 20.0% at a site in Ivory Coast (Abidjan), 16.1% at a site in Kenya (Siaya District), 24.3% at a site in Mali (Bougoula), 15% at a site in Gabon (Lambarene) and 3.7% (21 patients) were from a site in SE Asia, Philippines (Puerto Princesa).

There were approximately equal percentages of male and female subjects and mean age was 5 years old with 43.4% of patients less than 5 years = 232/535 ; PA: 160, AL: 72. Thirteen (13) were aged less than 1 year (PA: 10; AL= 3). All had less than 25 kg body weight.

Outcomes and estimation

Table 5: Day 28 PCR-corrected ACPR by Age category in EE population

Age Category Statistic	PA	AL	Difference in cure rate (PA minus AL) 95% CI ^a
<1 year of age			
Available observations	10	3	23.3
Number (%) of subjects cured	9 (90.0)	2 (66.7)	-17.5, 70.0
1-<5 years of age			
Available observations	140	61	-3.6
Number (%) of subjects cured	135 (96.4)	61 (100.0)	-8.1, 2.7
5-12 years of age			
Available observations	187	103	-0.1
Number (%) of subjects cured	185 (98.9)	102 (99.0)	-3.0, 4.3

a. 2-sided CI for between-group comparison calculated using Newcombe-Wilson method.

Cross Reference: [Statistical Table 14.2.1.1.2.](#)

Efficacy data (Day 42) are presented as follows:

Table 6: Day 42 PCR-corrected ACPR in the EE population and the ITT population- SP-C-007-07

	EE population		ITT population	
	Pyronaridine/Artesunate N=[275] n (%)	Artemether/Lumefantrine N=[139] n (%)	Pyronaridine/Artesunate N=[355] n (%)	Artemether/Lumefantrine N=[180] n (%)
Patients excluded from the EE population :	80 (22.5%)	41 (22.8%)	NA	NA
PCR-corrected ACPR on Day 42				
Available observations	275 (100%)	139 (100%)	255 (100%)	180 (100%)
Number of patients cured	257	133	262	135
Cure rate (%)	93.5	95.7	73.8	75.0
95% CI [*]	89.9; 96.1	90.8; 98.4	68.9; 78.3	68.0; 81.1
Between group comparison				
Difference	-2.2		-1.2	
95% CI ^{**}	-6.5; 1.3		-8.7; 6.9	
Conclusion from the applicant ^{***}	Non-inferiority		Non-inferiority	
Rapporteur's opinion ^{****}	Non-inferiority not recognised		Non-inferiority not recognised	
P-value ^{*****}	0.359		0.765	
Number of treatment failure	18 (6.5%)	6 (4.3%)	93 (26.2%)	45 (25.0%)
Early treatment failure	2 (0.7%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late clinical failure	2 (0.7%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late parasitological failure	14 (5.1%)	6 (4.3%)	14 (3.9%)	6 (3.3%)
Unknown (missing data) (a+b)	0 (0.0%)	0 (0.0%)	75 (21.1%)	39 (21.7%)
a) Previous New Infection	0 (0.0%)	0 (0.0%)	51 (14.4%)	26 (14.4%)
b) Other	0 (0.0%)	0 (0.0%)	24 (6.8%)	13 (7.2%)

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat,

PCR = polymerase chain reaction

Note: Percentages are based on available observations

Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.

* Exact two-sided 95% Confidence Interval (Pearson-Clopper)

** The two-sided Confidence Interval for between group comparison was calculated using Newcombe-Wilson method

*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -10%

**** The rapporteurs consider that the -10 % non inferiority limit is too low (see comment further below in the text)

*****Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Table 7: Day 42 Crude ACPR in the EE population and the ITT population-SP-C-007-07

	EE population		ITT population	
	Pyronaridine/Artesunate N=[325] n (%)	Artemether/Lumefantrine N=[166] n (%)	Pyronaridine/Artesunate N=[355] n (%)	Artemether/Lumefantrine N=[180] n (%)
Patients excluded from the EE population :	30 (8.4%)	14 (7.8%)	NA	NA
Crude ACPR on Day 42				
Available observations	325 (100%)	166 (100%)	355 (100%)	180 (100%)
Number of patients cured	249	130	254	132
Cure rate (%)	76.6	78.3	71.5	73.3
95% CI*	71.6; 81.1	71.3; 84.3	66.5; 76.2	66.2; 79.6
Between group comparison				
Difference	-1.7		-1.8	
95% CI**	-9.1; 6.4		-9.5; 6.4	
Conclusion from the applicant***	Non-inferiority		Non-inferiority	
Rapporteurs' opinion ****	Non-inferiority not recognised		Non-inferiority not recognised	
P-value*****	0.671		0.664	
Number of treatment failures	76 (23.4%)	36 (21.7%)	101 (28.5%)	48 (26.7%)
Early treatment failure	2 (0.6%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Late clinical failure	14 (4.3%)	5 (3.0%)	14 (3.9%)	5 (2.8%)
Late parasitological failure	60 (18.5%)	31 (18.7%)	61 (17.2%)	31 (17.2%)
Unknown (missing data) (a+b)	0 (0.0%)	0 (0.0%)	24 (6.8%)	12 (6.7%)
a) Previous New Infection	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
b) Other	0 (0.0%)	0 (0.0%)	23 (6.5%)	12 (6.7%)

ACPR = adequate clinical and. parasitological response, EE = efficacy evaluable, ITT = intent to treat, PCR = polymerase chain reaction

Note: Percentages are based on available observations

Patients who discontinued treatment due to an adverse event were classified as Early Treatment Failures according to a medical review.

* Exact two-sided 95% Confidence Interval (Pearson-Clopper)

** The two-sided Confidence Interval for between groups comparisons was calculated using Newcombe-Wilson method

*** Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the difference was above -10%

**** The rapporteurs consider that the -10 % non inferiority limit is too low (see comment further below in the text)

***** Two-sided Chi-square test for superiority (performed only when non-inferiority had been demonstrated)

Ancillary analyses

Based on Kaplan-Meier estimates, the cumulative risk of recrudescences through Day 42 was not statistically significant different between PA and AL groups ($p=0.5263$), neither with regards to new infection ($p=0.7740$), nor parasite re-appearance ($p=0.9800$). However, there was a tendency of higher recrudescence rate at Day 42 in the AL.

Of note, in the subgroup analysis at Day 42, children under 5 years and patients in Asia appeared to have the lowest cure rate. Noticeable lower cure rates (termed PCR-corrected ACPR) appear in children less than 5 years (in EE and ITT population) as compared to older i.e. 5 to 12 years age population.

The results in Asia were lower as compared to Africa countries in the ITT population (69.2% vs. 100% respectively) but as the sample size is small, power is limited.

In summary, in this study SP-C-007-07, the SOH has chosen a non-inferiority margin of -10% instead of -5% (as was employed in the other studies). However, this non inferiority limit is considered too low, in view of the high efficacy expected and cure rates appear very low ($< 90\%$) in the PA group with treatment failures/recrudescences consistently higher in the PA group as compared to the AL group.

Parasite clearance time:

Pyronaridine tetrphosphate/artesunate and AL were rapidly effective on parasitaemia. Parasite count decreased rapidly (during the first 16 hours) similarly in both the PA and AL groups.

Based on Kaplan-Meier estimates, time to parasite clearance was marginally statistically significantly ($p=0.0459$) shorter in the PA group compared with the AL group. In the EE population, a slightly higher percentage of PA vs. AL subjects achieved parasite clearance 24 hours after the first dose (49.9% vs. 43.7%). At 48 hours after first dosing 95.5 % and 95.2 % had achieved parasite clearance in the PA and AL group respectively, and at 72 hours after first dose results were 97.0 % vs. 98.8 % in PA and AL respectively. Median time to parasite clearance was 24.1 and 24.2 hours in the PA and AL groups, respectively.

Time to fever clearance was similar in the PA and AL groups. Most of patients took antipyretics.

Study n° SP-C-013-11

Paediatric sub-study analysis to provide additional efficacy and safety data of pyronaridine tetrphosphate / artesunate (PA) granules for the treatment of recurrent malaria episodes in children with a body weight from 5 kg to less than 20 kg.

Methods

Comparative, Randomised, Multi-centre, Open-Label, Parallel 3-arm Clinical Study to Assess the Safety and Efficacy of Repeated Administration of Pyronaridine-artesunate, Dihydroartemisinin-piperaquine or Artemether-lumefantrine or Artesunate-amodiaquine Over a 2-year Period in Children and Adult Patients with Acute Uncomplicated Plasmodium sp. Malaria

The WANECAM (SP-C-013-11) study is being conducted by 6 investigators at 6 study centres in 3 West African countries (Mali, Burkina Faso, and Republic of Guinea).

Study Participants

Children with a body weight from 5 kg to less than 20 kg who present uncomplicated malaria episodes.

Suitable patients who present to the participating study centre with symptoms of acute, uncomplicated malaria are assessed for eligibility. Patients whose eligibility is confirmed then enter the 3-day treatment phase.

Treatments

Pyramax®: pyronaridine tetrphosphate-artesunate (PA)

Depending on their body weight patients received a total of between 1 to a maximum of 4 tablets or 1 to 3 sachets per day administered at the same time of day (for 3 consecutive days). The dose in each tablet was 180:60 mg pyronaridine tetrphosphate: artesunate, and 60:20 mg for each granule sachet.

Oral PA tablets and granules for oral suspension:

- 1 sachet with granules from 5 to <8 kg
- 2 sachets with granules from 8 to <15 kg
- 3 sachets with granules from 15 to <20 kg
- (• 1 tablet from 20 to <24 kg
- 2 tablets from 24 to <45 kg)

For the paediatric granule formulation for oral suspension of PA in sachets: the content of one sachet was to be dissolved in a small amount of clean drinking water (about 10 mL per sachet) in the small cup provided, and subsequently administered orally under supervision; thereafter the cup/beaker was to be rinsed with an additional 10 mL of water and the content was to be swallowed again. This procedure was to be repeated as necessary in order to administer the amount of doses indicated.

Where the PA tablet formulation was administered, patients 20 kg and over were administered PA tablets to be swallowed whole with a small amount of clean drinking water under supervision.

Coartem®Dispersible and Coartem®: artemether-lumefantrine (AL)

Artemether-lumefantrine (AL) is administered twice daily for 3 days. The second dose was to be administered 8 hours (± 1 hour) after the first dose. The four other doses were given twice daily (morning and evening). A minimum of 8 hours was to be observed between 2 doses.

Ideally the doses were to be administered as follows after Dose 1: for Dose 2 (at Hour 8), the administration time window was not to be $> \pm 1$ hour. For the following doses at Hours 24, 36, 48, and 60 (twice daily), the time window was to be not $> \pm 2$ hours.

Depending on their body weight, patients received either Coartem Dispersible or Coartem tablets (both formulations containing 20 mg artemether and 120 mg lumefantrine per tablet):

- 1 dispersible tablet from 5 to <15 kg
- 2 dispersible tablets from 15 to <25 kg
- (• 3 tablets from 25 to <35 kg
- 4 tablets for ≥ 35 kg)

Objectives

The overall primary objective of the WANECAM study is to compare the incidence of uncomplicated malaria episodes in children and adults treated with ACT over a follow-up period of 2 years. In this 3 arm non-inferiority study, PA and DHA-PQP are compared to either ASAQ or AL (depending on the study centre location). Pyronaridine tetrphosphate/artesunate and DHA-PQP are not formally compared.

The primary objective of the present paediatric sub-study analysis is intended to provide additional efficacy and safety data of PA granules for the treatment of recurrent malaria episodes in children with a body weight from 5 kg to less than 20 kg in this WANECAM study. The sub-study analysis is intended to support a submission to EMA regarding the PA paediatric granule formulation (Pyramax Granules for Oral Suspension). Paediatric patients treated with AL were included in the analysis as reference treatment.

Outcomes/endpoints

Safety

- The occurrence of hepatotoxicity events, defined as alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN) or Hy's law (ALT or aspartate aminotransferase [AST] $>3 \times$ ULN and total bilirubin $>2 \times$ ULN) at any post-dose time point (the time point being discrete and following each treatment i.e., after the first dose, after the second dose, after the third dose, and so forth)
- Monitoring of adverse events (AEs), vital signs, safety laboratory parameters, and electrocardiogram (ECG)

Efficacy

- 28 day / 42 day crude adequate clinical and parasitological response (ACPR) and PCR-corrected ACPR rate using the WHO 2009 definition

- Parasite clearance time (PCT), defined as the time from first dose within the current episode until continued disappearance of asexual parasites which remains at least a further 48 hours
- Occurrence of fever (note that fever clearance time was not to be calculated, as there was only one body temperature assessment per day)
- Incidence of gametocyte occurrence and gametocyte carriage

The following efficacy endpoints were to be presented for the first treatment episode for patients in the ITT population with a *P. falciparum* infection using Kaplan-Meier estimates:

- Time until re-infection (= new infection)
- Time until recrudescence
- Time until recurrence (re-infection or recrudescence)

28-day / 42 day crude and PCR-corrected ACPR as well as PCT were to be further summarized for subgroups defined based on body weight (<8 kg, 8-<15 kg, 15-<20 kg).

These body weight subgroup categories correspond to the number of sachets administered for the weight range, being 1, 2 or 3 respectively.

Sample size

All efficacy analyses in this sub-study were descriptive. Thus, no separate sample size calculation was prepared for this sub-study. The initial sample size calculation was prepared to meet the objectives of the main study, i.e., to assess the non-inferiority of PA or DHA-PQP vs. ASAQ or AL in term of the incidence rate of uncomplicated malaria in children and adults treated with repeated ACT therapy over a 2 years observation period and to assess the non-inferiority of PA or DHA-PQP vs ASAQ or AL in term of PCR-corrected and uncorrected ACPR at Day 28 and Day 42.

Randomisation

At the first visit, all patients who fulfilled all the inclusion/exclusion criteria were given the lowest available number on the randomisation list. This number assigned them to one of the treatment arms. The investigator entered the randomisation number on the CRF. The randomisation numbers were generated to ensure that treatment assignment was unbiased. To ensure efficient use of experimental drug supplies, independent randomisation lists were produced by or under the responsibility of the sponsor using a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a Quality Assurance Group and locked by them after approval.

Blinding (masking)

This study was open-label. The microscopists in charge of reading malaria smears were to be kept blinded until the malaria smear results were available. Microscope slide smear readers were not to have access to the treatment record and were not to participate in the assessment and treatment of the participants. This was because the parasite outcome was very critical in determining the primary endpoint (malaria incidence) as well as the efficacy outcomes of the overall WANECAM study.

Statistical methods

The primary efficacy evaluable population (EE) was defined as all patients from the PA/AL arm weighing less than 20 kg:

– who completed a full course of study medication for a treatment episode and had a known primary efficacy endpoint at Day 28 of that episode. A patient was to be excluded from the EE analysis if the parasite count was missing at Day 28 and no subsequent parasite count was available after Day 28, and the patient was not previously classified as treatment failure. This included patients who discontinued from the study before Day 28 for any reason, as well as those who had a new infection, or a non *P. falciparum* infection before Day 28 and did not have any further parasite assessment. Note that the latter only applied for the analysis of PCR-corrected cure. In the EE analyses of crude cure patients with a new infection were to be included as treatment failure. The same methodology was to be applied for the classification of treatment outcome at Day 42.

– did not use a concomitant medication with known anti-malarial activity which could interfere with the treatment outcome up to Day 28, except if the treatment was given for the treatment of a new infection. In that case a patient was to be considered a failure in the EE analysis of crude cure and was to be excluded from the EE analysis of the PCR-corrected cure.

– had *P. falciparum* malaria for the episode of interest

– did not have major protocol deviations. The list of all protocol deviations was to be reviewed with respect to their impact (major/minor) prior to analysis.

The secondary efficacy evaluable population was defined in the same way as the primary efficacy evaluable population additionally taking into account PA patients from the PA/ASAQ arm.

Results

Participant flow

The sub-study analysis of **SP-C-013-11** for the < 20 kg patients includes all patients who received paediatric formulation of granules for oral suspension for the first treatment episode

Table 8: Patients treated with Pyramax <20 kg for first and consecutive episodes and time interval between episodes.

	Pyronaridine/Artesunate		Artemether/Lumefantrine	
Episode 1	n=376		n=233	
< 20 kg	376	100%	233	100%
Episode 2				
< 20 kg	124	100%	84	100%
Median time between Ep 1 and 2 (Days)	49.0		43.5	
Episode 3				
< 20 kg	35	100%	20	100%
Median time between Ep 2 and 3 (Days)	43.0		44.0	
Episode 4				
< 20 kg	9	100%	2	100%
Median time between Ep 3 and 4 (Days)	41		35.0	
Episode 5				

	Pyronaridine/Artesunate	Artemether/Lumefantrine		
< 20 kg	2	100%		
Median time between Ep 4 and 5 (Days)	33.5			

In this sub-study, 376 paediatric patients <20 kg were treated with Pyramax granules for oral suspension and 233 patients were treated with Artemether/Lumefantrine orodispersable tablets for their first malaria episode. For the second malaria episode 124 patients were treated with PA and 84 with AL. For episodes 3 -5, the number of patients is low.

(NOTE: Overall in Study SP-C-013-11, 1015 patients were treated with PA. 393 patients <20 kg were treated with granules for suspension. It should be noted that 17 patients treated with granules were not children and these are not taken into account for the current line extension.)

Recruitment

The study report states that first patient enrolled on 12 November 2012 and last patient completed on 12 December 2013.

Conduct of the study

The original protocol (Version 1.1) was dated 19 November 2010.

Amendments that were instituted in Mali were implemented with protocols Version 4.0 (14 July 2011), Version 5.0 (20 October 2011), Version 6.0 (14 December 2011), Version 7 (29 May 2012), Version 9.0 (30 August 2013), and Version 10.0 (16 October 2013).

Amendments that were instituted in Burkina Faso were implemented with protocols Version 4.0 (14 July 2011), Version 6.0 (14 December 2011), and Version 8.0 (26 October 2012).

The amendment that was instituted in Republic of Guinea was implemented with protocol Version 8.0 (26 October 2012).

At the time of the data cut-off for the sub-study, Version 10.0 of the protocol was approved in Mali and Burkina Faso and under review in Republic of Guinea.

Baseline data

The mean age and body mass index (BMI), percentage of patients in each age category (≤ 6 months, >6 months - <1 year, 1-2 years, 3-5 years, ≥ 6 years), and distribution of males and females were similar between the treatment arms. Data from the repeat dose safety population were similar.

Table 9

Variable/ Statistic/Category	Pyronaridine artesunate (N=376)	Artemether lumefantrine (N=233)	Total (N=609)
Height (cm)			
Available observations	376	233	609
Mean	100.1	102.5	101.1
Standard deviation	11.98	11.20	11.74
Minimum	65.0	70.2	65.0
Q1	91.6	94.0	93.0
Median	101.4	103.8	102.0
Q3	109.5	111.0	110.4
Maximum	124.3	123.0	124.3
Body weight (kg)			
Available observations	376	233	609
Mean	14.6	15.0	14.7
Standard deviation	3.15	2.76	3.01
Minimum	6.7	7.8	6.7
Q1	12.3	12.9	12.6
Median	14.9	15.3	15.0
Q3	17.2	17.2	17.2
Maximum	19.8	19.8	19.8
Body weight category, n (%)			
5-<8 kg	4 (1.1)	1 (0.4)	5 (0.8)
8-<15 kg	186 (49.5)	105 (45.1)	291 (47.8)
15-<20 kg	186 (49.5)	127 (54.5)	313 (51.4)
Body mass index (kg/m ²)			
Available observations	376	233	609
Mean	14.45	14.24	14.37
Standard deviation	1.293	1.265	1.285
Minimum	10.5	8.0	8.0
Q1	13.63	13.35	13.53
Median	14.33	14.17	14.26
Q3	15.32	15.12	15.24
Maximum	18.6	17.6	18.6

Missing values were not included in the calculation of percentages.

Table 10: Baseline Plasmodium falciparum Parasite Counts (Safety population)

Variable/ Statistic/Category	Pyronaridine artesunate (N=376)	Artemether lumefantrine (N=233)	Total (N=609)
Number (%) of patients at Day 0 of first episode who have			
P. falciparum asexual forms	372 (98.9)	233 (100.0)	605 (99.3)
P. falciparum gametocytes	6 (1.6)	6 (2.6)	12 (2.0)
P. ovale asexual forms	1 (0.3)	1 (0.4)	2 (0.3)
P. ovale gametocytes	1 (0.3)	0 (0.0)	1 (0.2)
P. malariae asexual forms	10 (2.7)	5 (2.1)	15 (2.5)
P. malariae gametocytes	1 (0.3)	0 (0.0)	1 (0.2)
P. falciparum asexual forms at Day 0 of first episode (/uL)			
Available observations	372	233	605
Geometric mean *	15525.9	22043.0	17769.6
Mean	48695.7	58737.5	52563.0
Standard deviation	51721.0	58226.0	54491.0
Minimum	40	16	16
Q1	4930.0	11360.0	6280.0
Median	28200.0	42000.0	33580.0
Q3	81810.0	90120.0	82760.0
Maximum	198960	279000	279000

* Geometric mean was only calculated if all counts were > 0.

Outcomes and estimation

Table 11: Day 28 PCR-corrected Adequate Clinical and Parasitological Response Rate by treatment episode and by body weight category (Intent-to-treat population)

Trt epi	Statistic	Body weight <8 kg		Body weight 8-<15 kg		Body weight 15-<20 kg	
		Pyronaridine artesunate (N=4)	Artemether lumefantrine (N=1)	Pyronaridine artesunate (N=186)	Artemether lumefantrine (N=105)	Pyronaridine artesunate (N=186)	Artemether lumefantrine (N=127)
1	Available observations	4	1	183	105	185	127
	Number (%) of patients with ACPR	4 (100.0)	1 (100.0)	166 (90.7)	85 (81.0)	177 (95.7)	103 (81.1)
	95% confidence interval (Pearson Clopper)	39.8-100.0	2.5-100.0	85.5- 94.5	72.1- 88.0	91.7- 98.1	73.2- 87.5
	Number (%) of treatment failures	0 (0.0)	0 (0.0)	17 (9.3)	20 (19.0)	8 (4.3)	24 (18.9)
	Early treatment failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Late clinical failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.8)
	Late parasitological failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
	Rescue med/unknown (missing data) #	0 (0.0)	0 (0.0)	12 (6.6)	3 (2.9)	8 (4.3)	4 (3.1)
	New infection before Day 28	0 (0.0)	0 (0.0)	5 (2.7)	16 (15.2)	0 (0.0)	18 (14.2)
2	Available observations	2	0	60	40	59	44
	Number (%) of patients with ACPR	2 (100.0)		56 (93.3)	33 (82.5)	56 (94.9)	37 (84.1)
	95% confidence interval (Pearson Clopper)	15.8-100.0		83.8- 98.2	67.2- 92.7	85.9- 98.9	69.9- 93.4
	Number (%) of treatment failures	0 (0.0)		4 (6.7)	7 (17.5)	3 (5.1)	7 (15.9)
	Early treatment failure	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Late clinical failure	0 (0.0)		1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
	Late parasitological failure	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Rescue med/unknown (missing data) #	0 (0.0)		1 (1.7)	0 (0.0)	2 (3.4)	0 (0.0)
	New infection before Day 28	0 (0.0)		2 (3.3)	7 (17.5)	1 (1.7)	7 (15.9)

Patients with no *P. falciparum* asexual forms at Day 0 are not taken into account for cure calculation.
Includes patients with missing data, or who received rescue medication due to vomiting of study drug.

Trt epi	Statistic	Body weight <8 kg		Body weight 8-<15 kg		Body weight 15-<20 kg	
		Pyronaridine artesunate (N=4)	Artemether lumefantrine (N=1)	Pyronaridine artesunate (N=186)	Artemether lumefantrine (N=105)	Pyronaridine artesunate (N=186)	Artemether lumefantrine (N=127)
3	Available observations	1	0	18	9	16	11
	Number (%) of patients with ACPR	1 (100.0)		16 (88.9)	7 (77.8)	16 (100.0)	7 (63.6)
	95% confidence interval (Pearson Clopper)	2.5-100.0		65.3- 98.6	40.0- 97.2	79.4-100.0	30.8- 89.1
	Number (%) of treatment failures	0 (0.0)		2 (11.1)	2 (22.2)	0 (0.0)	4 (36.4)
	Early treatment failure	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Late clinical failure	0 (0.0)		1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Late parasitological failure	0 (0.0)		0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)
	Rescue med/unknown (missing data) #	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
	New infection before Day 28	0 (0.0)		1 (5.6)	1 (11.1)	0 (0.0)	3 (27.3)
4	Available observations	0	0	3	2	6	0
	Number (%) of patients with ACPR			3 (100.0)	1 (50.0)	6 (100.0)	
	95% confidence interval (Pearson Clopper)			29.2-100.0	1.3- 98.7	54.1-100.0	
	Number (%) of treatment failures			0 (0.0)	1 (50.0)	0 (0.0)	
	Early treatment failure			0 (0.0)	0 (0.0)	0 (0.0)	
	Late clinical failure			0 (0.0)	0 (0.0)	0 (0.0)	
	Late parasitological failure			0 (0.0)	0 (0.0)	0 (0.0)	
	Rescue med/unknown (missing data) #			0 (0.0)	0 (0.0)	0 (0.0)	
	New infection before Day 28			0 (0.0)	1 (50.0)	0 (0.0)	

Patients with no *P. falciparum* asexual forms at Day 0 are not taken into account for cure calculation.
Includes patients with missing data, or who received rescue medication due to vomiting of study drug.

Ancillary analyses

Parasite Clearance Time

Parasite clearance time (PCT) was defined as the time from first dose within the current episode until continued disappearance of asexual parasites which remained at least a further 48 hours. The Kaplan-Meier estimates for the intent-to-treat population, primary efficacy evaluable population and secondary efficacy evaluable population have been presented including by weight category. The *P. falciparum* parasite clearance by 72 hours was almost complete in the first two treatment episodes and complete at episodes 3 to 5. The PCT was similar between treatment episodes in the PA arm. Body weight category appeared to have no impact on PCT.

The median PCT was marginally shorter in the PA (34.1 hrs) arm than in the AL arm (35.3 hrs) during treatment episode 1 and was similar during the other treatment episodes. The clearance rate was complete or almost complete by 72 hours in both the PA and AL arms. Body weight category appeared to have no impact on PCT in either treatment arm.

Occurrence of fever

On Day 2 post-baseline of each episode, almost no patients with fever were recorded in the PA and AL arms. The range of patients presenting with no fever by Day 3 was 91.2% to 100.0% in both treatment arms from episodes 1 to 3. The results were very similar in the primary efficacy evaluable population and the secondary efficacy evaluable population.

Gametocytes

The percentage of patients with *P. falciparum* gametocytes at baseline showed a gradual decrease to zero in patients, whereas in patients without gametocytes at baseline the counts rose initially and then gradually decreased to zero over time in both treatment arms of the primary efficacy evaluable population. No gametocytes were detected in the primary efficacy evaluable population in either treatment arm after episode 2. In the secondary efficacy evaluable population, few patients had gametocytes detected at baseline (6/343 patients [1.7%] in the PA arm and 6/190 patients [3.2%] in the AL arm at episode 1). The percentage of patients with gametocytes rose initially then gradually decreased to zero over time in both arms during each episode. No gametocytes were detected in the secondary efficacy evaluable population after episode 3 in either treatment arm.

Time until recurrence, recrudescence, and re-infection

Kaplan-Meier estimates for time until recurrence and recrudescence were calculated and presented for time to recurrence. Time to recurrence of *P. falciparum* infection was statistically significantly longer in the PA arm compared to the AL arm during the first 2 episodes (episode 1: $p < 0.0001$, episode 2: $p = 0.0182$, log rank test), whereas recrudescence showed no statistically significant difference between treatment groups for any episode.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12. Summary of Efficacy for trial SP-C-007-07

Title: A Phase III comparative, open-labelled, randomised, multi-centre clinical study to assess safety and efficacy of a fixed dose of oral pyronaridine artesunate granule formulation (60:20 mg) (paediatric PYRAMAX®) versus Coartem® (artemether lumefantrine) crushed tablets in infants and children with acute uncomplicated <i>Plasmodium falciparum</i> malaria			
Study identifier	SP-C-007-07		
Design	multicentre, comparative, randomised, open-labelled, parallel group study		
	Duration of main phase:		42 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Non-inferiority		
Treatments groups	PA		Pyronaridine/Artesunate, 3 days, 355
	AL		Artemether/Lumefantrine, 3 days, 180
Endpoints and definitions	Primary endpoint	P1	PCR-corrected ACPR at Day 28 in the PA group <=90% (EE population)
	Secondary endpoints	S1: COR-EE-D28 COR-ITT-D28	Day 28 PCR-corrected ACPR in EE and ITT populations
		S2: COR-<POP>-<DAY>	PCR-corrected ACPR at days 14 and 42 in EE and ITT populations
		S3: CRU-<POP>-<DAY>	Crude cure rate at days 14, 28 and 42 in EE and ITT populations
		S4	Proportion of aparasitaemic patients and time to parasite clearance
		S5	Proportion of afebrile patients and time to fever clearance
		S6	Proportion of patients with gametocytes by time points
Database lock	26 November 2008		

Results and Analysis

Analysis description	Primary Analysis P1		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	339	167
	COR-EE-D28 (N (%))	329 (97.1%)	165 (98.8%)
Effect estimate per comparison	Primary endpoint	p-value *	<0.001
Notes	* For the hypothesis that the ACPR in the PA group is $\leq 90\%$		
Analysis description	Secondary analysis S1: COR-EE-D28, COR-ITT-D28		
Analysis population and time point description	Efficacy Evaluable population Day 28		

Descriptive statistics	Treatment group	PA	AL
	Number of subjects	339	167
	COR-EE-D28 (N (%))	329 (97.1%)	165 (98.8%)
Effect estimate per comparison	Between group comparison	Comparison groups	PA – AL
		Difference	-1.8
		95% two-sided CI	-4.3 ; 1.6
		p-value *	0.223
Notes	* Two-sided Chi-Square test for superiority CI = Confidence Interval		
Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D28 (N (%))	333 (93.8%)	167 (92.8%)
Effect estimate per comparison	Between group comparison	p-value *	0.008
		Comparison groups	PA – AL
		Difference	1.0
		95% two-sided CI	-3.2 ; 6.2
		p-value **	0.651
Notes	* For the hypothesis that the ACPR in the PA group is $\leq 90\%$ ** Two-sided Chi-Square test for superiority CI = Confidence Interval		
Analysis description	Secondary analysis S2: COR-EE-D14, COR-EE-D42 COR-ITT-D14, COR-ITT-D42		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	343	172
	COR-EE-D14 (N (%))	341 (99.4%)	172 (100%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-2.1 ; 1.6
		p-value	0.316
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL

	Number of subjects	275	139
	COR-EE-D42 (N (%))	257 (93.5%)	133 (95.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-2.2
		95% two-sided CI	-6.5 ; 3.1
		p-value	0.359
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D14 (N (%))	344 (96.9%)	174 (96.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.2
		95% two-sided CI	-2.7 ; 4.2
		p-value	0.884
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	COR-ITT-D42 (N (%))	262 (73.8%)	135 (75.0%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.2
		95% two-sided CI	-8.7 ; 6.9
		p-value	0.765
Notes	CI = Confidence Interval		
Analysis description	Secondary analysis S3: CRU-EE-D14, CRU-EE-D28, CRU-EE-D42 CRU-ITT-D14, CRU-ITT-D28, CRU-ITT-D42		
Analysis population and time point description	Efficacy Evaluable population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	343	172
	CRU-EE-D14 (N (%))	341 (99.4%)	172 (100%)

Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-0.6
		95% two-sided CI	-2.1 ; 1.6
		p-value	0.316
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	341	172
	CRU-EE-D28 (N (%))	305 (89.4%)	149 (86.6%)
Effect estimate per comparison		Comparison groups	AL
		Difference	2.8
		95% two-sided CI	-2.9 ; 9.4
		p-value	0.345
Notes	CI = Confidence Interval		
Analysis population and time point description	Efficacy Evaluable population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	325	166
	CRU-EE-D42 (N (%))	249 (76.6%)	130 (78.3%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.7
		95% two-sided CI	-9.1 ; 6.4
		p-value	0.671
Analysis population and time point description	ITT population Day 14		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D14 (N (%))	344 (96.9%)	174 (96.7%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	0.2
		95% two-sided CI	-2.7 ; 4.2
		p-value	0.884
Notes	CI = Confidence Interval		

Analysis population and time point description	ITT population Day 28		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D28 (N (%))	309 (87.0%)	151 (83.9%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	3.2
		95% two-sided CI	-2.9 ; 10.0
		p-value	0.321
Notes	CI = Confidence Interval		
Analysis population and time point description	ITT population Day 42		
Descriptive statistics	Treatment group	PA	AL
	Number of subjects	355	180
	CRU-ITT-D42 (N (%))	254 (71.5%)	132 (73.3%)
Effect estimate per comparison		Comparison groups	PA – AL
		Difference	-1.8
		95% two-sided CI	-9.5 ; 6.4
		p-value	0.664
Analysis description	Secondary analysis S4: Proportion of aparasitaemic patients and time to parasite clearance		
Analysis population and time point description	ITT population		
Kaplan-Meier estimate	Treatment group	PA	AL
	Number of subjects	355	180
	Aparasitaemic at Day 1 (% (95% CI))	49.3 (44.1 ; 54.5)	41.7 (34.5 ; 48.9)
	Aparasitaemic at Day 2 (% (95% CI))	94.6 (92.3 ; 97.0)	93.3 (89.7 ; 97.0)
	Aparasitaemic at Day 3 (% (95% CI))	96.1 (94.0 ; 98.1)	97.2 (94.8 ; 99.6)
	Median time to parasite clearance (hours (95% CI))	24.1 (24.0 ; 24.1)	24.2 (24.1 ; 32.0)
Notes	CI = Confidence Interval		
Analysis description	Secondary analysis S5: Proportion of afebrile patients and time to fever clearance		
Analysis population and time point description	ITT population		
Kaplan-Meier	Treatment group	PA	AL

estimate	Available observations	278	135
	Afebrile at Day 1 (% (95% CI))	86.3 (82.3 ; 90.4)	79.3 (72.4 ; 86.1)
	Afebrile at Day 2 (% (95% CI))	97.5 (95.6 ; 99.3)	94.1 (90.1 ; 98.1)
	Afebrile at Day 3 (% (95% CI))	98.6 (97.2 ; 100)	95.6 (92.1 ; 99.0)
	Median time to fever clearance (hours (95% CI))	8.1 (8.0 ; 8.1)	8.1 (8.0 ; 15.8)
Notes	CI = Confidence Interval Available observations = Subjects in the ITT population with fever at baseline		
Analysis description	Secondary analysis S6: Proportion of patients with gametocytes by time points		
Analysis population and time point description	ITT population		
Descriptive statistics	Treatment group	PA	AL
Number of subjects with gametocytes (N (%))	Number of subjects	355	180
	Baseline	44 (12.4%)	26 (14.4%)
	>0-24 hours	73 (20.6%)	39 (21.9%)
	>24-48 hours	63 (19.3%)	23 (13.4%)
	>48-72 hours	40 (15.1%)	16 (11.9%)
	>72 hours – Day 5	20 (18.0%)	6 (10.0%)
	Day 6 – 12	45 (13.0%)	16 (9.2%)
	Day 13 – 16	28 (8.3%)	6 (3.5%)
	Day 17 – 26	15 (4.5%)	2 (1.2%)
	Day 27 – 30	3 (0.9%)	2 (1.2%)
	Day 31 – 40	1 (0.3%)	0
	Day 41 – 44	0	0
	>Day 44	0	0
	Any post-baseline	95 (26.8%)	44 (24.7%)
	Any post-baseline (new occurrence)	53 (15.0%)	20 (11.2%)
Analysis population and time point description	Efficacy Evaluable population		
Descriptive statistics	Treatment group	PA	AL
Number of subjects with gametocytes (N (%))	Number of subjects	337	167
	Baseline	43 (12.8%)	24 (14.4%)
	>0-24 hours	71 (21.1%)	35 (21.0%)
	>24-48 hours	62 (19.9%)	22 (13.6%)
	>48-72 hours	40 (15.6%)	15 (11.7%)
	>72 hours – Day 5	19 (17.9%)	6 (10.9%)
	Day 6 – 12	44 (13.1%)	16 (9.6%)
	Day 13 – 16	28 (8.5%)	6 (3.6%)

	Day 17 – 26	15 (4.5%)	2 (1.2%)
	Day 27 – 30	3 (0.9%)	2 (1.2%)
	Day 31 – 40	1 (0.3%)	0
	Day 41 – 44	0	0
	>Day 44	0	0
	Any post-baseline	92 (27.3%)	40 (24.0%)
	Any post-baseline (new occurrence)	51 (15.1%)	18 (10.8%)

Analysis description	Primary analysis			
Analysis population and time point description	Efficacy - Day 28 PCR-Corrected ACPR- EE by age category D28			
Descriptive statistics and estimate variability	Treatment group	PA	AL	Difference in cure rate (PA minus AL) 95% CI*
	<1 year of age Available observations Number (%) of subjects cured	10 9 (90)	3 2 (66.7)	23.3 -17.5, 70.0
	1-<5 years of age Available observations Number (%) of subjects cured	140 135 (96.4)	61 61 (100.0)	-3.6 -8.1, 2.7
	5-12 years of age Available observations Number (%) of subjects cured	187 185 (98.9)	103 102 (99.0)	-0.1 -3.0, 4.3
Note	a. 2-sided CI for between-group comparison calculated using Newcombe-Wilson method			

Table 13. Summary of Efficacy for trial SP-C-013-11

<i>Paediatric sub-study analysis to provide additional efficacy and safety data of pyronaridine tetraphosphate / artesunate (PA) granules for the treatment of recurrent malaria episodes in children with a body weight from 5 kg to less than 20 kg.</i>		
Study identifier	SP-C-013-11	
Design	Comparative, Randomised, Multi-centre, Open-Label, Parallel 3-arm Clinical Study	
	Duration of main phase:	42 days
	Duration of run-in phase:	not applicable
	Duration of extension phase:	not applicable
Hypothesis	Efficacy analyses were performed for the intent-to-treat population and for the primary and secondary efficacy evaluable populations. All efficacy analyses were descriptive. There was no formal statistical testing within this sub-study analysis, however 95% confidence intervals for treatment group differences were provided for selected variables.	
Treatment groups	PA	Pyronaridine/ Artesunate, 3 days
	AL	artemether-lumefantrine, 3 days
Endpoints and definitions	<u>Safety</u> - The occurrence of hepatotoxicity events, defined as alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN) or Hy's law (ALT or aspartate aminotransferase [AST] >3 x ULN and total bilirubin >2 x ULN) at any post-dose time point (the time point being discrete and following each treatment i.e., after the first dose, after the second dose, after the third dose, and so forth) - Monitoring of adverse events (AEs), vital signs, safety laboratory parameters, and electrocardiogram (ECG) <u>Efficacy</u> - 28 day / 42 day crude adequate clinical and parasitological response (ACPR) and PCR-corrected ACPR rate using the WHO 2009 definition - Parasite clearance time (PCT), defined as the time from first dose within the current episode until continued disappearance of asexual parasites which remains at least a further 48 hours - Occurrence of fever (note that fever clearance time was not to be calculated, as there was only one body temperature assessment per day) - Incidence of gametocyte occurrence and gametocyte carriage The following efficacy endpoints were to be presented for the first treatment episode for patients in the ITT population with a <i>P. falciparum</i> infection using Kaplan-Meier estimates: - Time until re-infection (= new infection) - Time until recrudescence - Time until recurrence (re-infection or recrudescence)	

Results and analysis			
Analysis description	Primary analysis		
Analysis population and time point description	Efficacy - Intent to treat – treatment Episode 1 D28		
Descriptive statistics and estimate variability	Treatment group	PA	AL
	D28 PCR-cor (ITT) Body weight 5-8Kg N(%) 95% confidence interval	4 (100) 39.8-100.0	1 (100) 2.5-100.0
	D28 PCR-cor (ITT) Body weight 8-15Kg N(%) 95% confidence interval	166 (90.7) 85.5- 94.5	85 (81) 72.1- 88.0
	D28 PCR-cor (ITT) Body weight 15-20Kg N(%) 95% confidence interval	177 (95.7) 91.7- 98.1	103 (81.1) 73.2- 87.5
Analysis population and time point description	Efficacy - Intent to treat – treatment Episode 2 D28		
Descriptive statistics and estimate variability	Treatment group	PA	AL
	D28 PCR-cor (ITT) Body weight 5-8Kg N(%) 95% confidence interval	2 (100) 15.8-100.0	0
	D28 PCR-cor (ITT) Body weight 8-15Kg N(%) 95% confidence interval	59 (93.3) 83.8- 98.2	33 (82.5) 67.2- 92.7
	D28 PCR-cor (ITT) Body weight 15-20Kg N(%) 95% confidence interval	56 (94.9) 85.9- 98.9	37 (84.1) 69.9- 93.4
Analysis population and time point description	Efficacy - Intent to treat – treatment Episode 3 D28		
Descriptive statistics and estimate variability	Treatment group	PA	AL
	D28 PCR-cor (ITT) Body weight 5-8Kg N(%) 95% confidence interval	1 (100) 2.5-100.0	0
	D28 PCR-cor (ITT) Body weight 8-15Kg N(%) 95% confidence interval	16 (88.9) 65.3- 98.6	7 (77.8) 40-97.2

	D28 PCR-cor (ITT) Body weight 15-20Kg N(%) 95% confidence interval	16 (100) 79.4-100	7 (63.6) 30.8-89.1	
Analysis population and time point description	Efficacy - Intent to treat – treatment Episode 4 D28			
Descriptive statistics and estimate variability	Treatment group	PA	AL	
	D28 PCR-cor (ITT) Body weight 5-8Kg N(%) 95% confidence interval	0	0	
	D28 PCR-cor (ITT) Body weight 8-15Kg N(%) 95% confidence interval	3 (100) 29.2- 100	1 (50) 1.3-98.7	
	D28 PCR-cor (ITT) Body weight 15-20Kg N(%) 95% confidence interval	6 (100) 54.1-100	0	
Note	95% confidence interval (Pearson Clopper)			
Analysis population and time point description	Efficacy - Day 28 PCR-Corrected ACPR- EE D28			
Descriptive statistics and estimate variability	Treatment group	PA	AL	Difference estimate for PA mins AL
	Number of patients	190	191	
	Total number of episodes	276	274	
	ACPR estimate 95% confidence interval	99.6 98.9-100	98.5 97.1-100	1.1 0-2.7
Notes	28 day / 42 day crude adequate clinical and parasitological response (ACPR) and PCR-corrected ACPR rate using the WHO 2009 definition			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The present data were part of an ongoing study SP-C-013-11 comparative multicentre trial studying the efficacy and safety of PA compared to AL in single and multi-episode malaria infection. The study is conducted in an area of medium transmission rate and moderate to high malaria endemicity in West Africa. The overall study comprises a total of 1015 patients treated with PA and 671 patients treated with AL. In total 376 patients (<20 kg) treated with PA and 233 patients (<20 kg) treated with AL were included in the current sub-analysis which serves as substantiation for the line extension. All patients received at least one treatment course for one malaria episode. Data for multiple malaria episodes were also provided.

Efficacy data and additional analyses

It is important to note that the qualitative and quantitative composition of the granules significantly differs from tablets and bioequivalence of the granules for oral suspension to the tablets has not been established. No definite conclusion on the bioequivalence of PA granules for oral suspension to PA tablets can be made as no specific bioequivalent study in malaria patients has been conducted. Therefore the efficacy of the granules for oral suspension completely relies on the data provided from this paediatric sub study and the data from the study SP-C-007-07 submitted in the line extension dossier. There is no pivotal clinical study to demonstrate that the efficacy of granules for oral suspension and the tablets are similar. Therefore only an indirect comparison can be made for which study SP-C-013-11 and SP-C-007-07 are crucial.

Data on the PCR-adjusted ACPR at day 28 in paediatric patients demonstrates that after treatment of malaria episode one efficacy of PA is better than AL (PA: 347/376 patients (93.3%); AL: 189/233 patients (81.1%) respectively). Similar results were shown when the data was stratified by weight categories (<8 kg; 8 to 15 kg, and 15 to <20 kg). Efficacy was maintained in other episodes but patient numbers are too small to draw firm conclusions. To add the study was not powered for efficacy (secondary end point). When comparing the efficacy data of PA in patients <20kg to patients ≥20 kg efficacy for PCR-adjusted ACPR at day 28 was similar (<20 kg: 93.1%; ≥20 kg: 96.6%).

Efficacy results in paediatrics for PCR adjusted ACPR at day 28 from study SP-C-013-11 were lower than the results observed in the initial Scientific Opinion study SP-C-007-07 (efficacy was in the order of 95-99% in both treatment arms). These differences (markedly in ITT analysis) could partly be explained by different timing and geographic location of the studies. Overall it can be asserted that despite the observed lower exposure to artesunate granules in healthy volunteers, efficacy results from the current study SP-C-013-11 suggest that in malaria infected patients treated with PA granules, this does not translate into a worse efficacy.

In the subgroup of children concerned by the line extension of the granule formulation, some reassurance has been gained on the efficacy of retreatment, with 124 children from 5 to 20 kg being retreated once, including 59 children from 8-15 kg and 56 children from 15-20 kg, but data are more limited for episodes>2 (around 30 children in episode 3).

Additional expert consultation

The benefit of Pyramax in children below 1 year of age could not be documented, with clinical data only derived from 20 patients (from both studies SP-C-007-07 and SP-C-013-11). Hence, experts were

consulted on the appropriateness to extend the indication to the subgroup of younger children (1 year old, < 10 kg). The minutes of the meeting are appended to this report (Annex 8).

The experts expressed the opinion that body weight of 5kg should be considered as cut-off, in line with the weight limit stated for other antimalarial agents. More data on the above stated uncertainties will become available from a proposed phase IV study (see RMP). They also confirmed that in line with the above consideration, children younger than 1 year old, < 10 kg could be included in the indication (extension cut-off at 5kg body weight), with proviso that the risk management plan is robust, and that the proposed post-marketing study be carried out.

2.5.4. Conclusions on the clinical efficacy

Only sparse clinical data have been obtained in children below 1 year of age. Nevertheless, body weight of 5kg should be considered as cut-off for the requested indication, in line with the weight limit stated for other antimalarial agents. More data on the above stated uncertainties will become available from proposed phase IV study, SP-C- 021-15. In addition, the SOH intends to conduct a study in western Kenya, comparing (safety and) efficacy of Pyramax granules with artemether-lumefantrine in paediatric population [aged 6 months (and ≥ 5 kg) to 12 years], suffering uncomplicated falciparum malaria (SP-C-020-15). These studies are detailed in the risk management plan.

2.6. Clinical safety

Introduction

The salient aspect of Pyramax safety profile remains the increase in liver transaminases, exacerbation of anaemia, neutropenia, vomiting, diarrhoea, interaction with drugs metabolised through CYP2D6 or via P-gp efflux. Regarding hepatotoxicity related to pyronaridine component, cytotoxicity may be dependent on the intracellular glutathione level or the glutathione redox cycle and may be caused by oxidative damage. The suggested potential dose-dependant hepatotoxicity of pyronaridine could be linked, as paracetamol, to the formation of a hepatotoxic reactive metabolite which could be detoxified by GSH. Then, in case of depletion of glutathione, inhibition of mitochondrial respiration occurred with hepatic damage such as cytolytic hepatitis.

Regarding safety supporting data in the frame of granules formulation line extension in children weighting between 5 and 20 kg, the SOH pooled in a population called "ISS Granules", the safety data regarding children who were exposed to PA granules.

Patient exposure

In the ISS for Granules population, including 667 patients who received the Pyramax granules is derived from different studies as follows:

Table 13: Patient numbers making up the Pyramax granules population

Study	PA	AL
SP-C-003-05	14	0
SP-C-007-07	277	125

SP-C-013-11	376	233
Total	667	358

Table 14: Demographic and baseline characteristics – Granules ISS population

Variable/ Statistic/Category	PA (N=667)	AL (N=358)
Gender, n (%)		
Male	310 (46.5)	183 (51.1)
Female	357 (53.5)	175 (48.9)
Age (years)		
Available observations	667	358
Mean	4.1	4.3
Standard deviation	1.95	1.96
Minimum	0	0
Q1	3	3
Median	4	4
Q3	5	5
Maximum	10	11
Age category, n (%)		
≤6 months	4 (0.6)	3 (0.8)
>6 months - <1 year	16 (2.4)	5 (1.4)
1-2 years	131 (19.6)	55 (15.4)
3-5 years	370 (55.5)	206 (57.5)
≥6 years	146 (21.9)	89 (24.9)
Height (cm)		
Available observations	661	355
Mean	100	101.5
Standard deviation	12.34	11.53
Minimum	60	69
Q1	92.4	93
Median	101	102.6
Q3	109.4	110.1
Maximum	128	130
Body weight (kg)		
Available observations	667	358
Mean	14.6	14.9
Standard deviation	3.09	2.81
Minimum	6	7.2
Q1	12.3	13
Median	15	15.1
Q3	17.1	17
Maximum	19.9	19.9

Most of exposed children aged from 3 years old (y/o), including 370 children between 3-5 y/o receiving PA. There were 131 children aged between 1-2 y/o. The mean weight is 14.6 kg and ranges from 6 kg to 19.9 kg. It should be stressed that weight can vary for a same age in a child, notably depending gender, especially below 2 y of age.

The cumulative numbers of patients weighing <8kg (n=7) and patients aged <1 y/o (n=20) are very limited.

Regarding repeated dosage, among all exposed patients between 5-20kg to PA granules in SP-C-013-11 study, 124 children were dosed at least twice and 35 patients at least 3 times. The median time for redosing in those patients who required a repeat dose was 41 to 49 days for each episode. This short delay of PA re-administration underlines a real medical need in this very young population and can be considered as relevant for a potential risk of pyronaridine accumulation.

Adverse events

Table 1 provides an overview of adverse event that occurred in $\geq 2\%$ of patients in the all paediatric patient population treated with the granules for oral suspension (Granules ISS population).

Table 1: Incidence of Adverse Events Reported by at least 2% of Patients in any Treatment Arm by Primary System Organ Class and Preferred Term – Granules ISS Population.

Primary system organ class	PA	AL	
Preferred term	n (%)	n (%)	p-value
Patients dosed	667 (100.0)	358 (100.0)	
At least one adverse event	426 (63.9)	222 (62.0)	0.5869
Blood and lymphatic system disorders	69 (10.3)	48 (13.4)	0.1498
Anaemia	35 (5.2)	17 (4.7)	0.7677
Neutropenia	15 (2.2)	11 (3.1)	0.4133
Monocytosis	10 (1.5)	10 (2.8)	0.1616
Gastrointestinal disorders	83 (12.4)	33 (9.2)	0.1473
Vomiting	52 (7.8)	12 (3.4)	0.0043
Abdominal pain	15 (2.2)	7 (2.0)	0.8252
General disorders and administration site conditions	41 (6.1)	11 (3.1)	0.0361
Pyrexia	20 (3.0)	7 (2.0)	0.4145
Influenza like illness	17 (2.5)	4 (1.1)	0.1652
Infections and infestations	230 (34.5)	115 (32.1)	0.4882
Bronchitis	93 (13.9)	53 (14.8)	0.7085
Rhinitis	38 (5.7)	27 (7.5)	0.2822
Upper respiratory tract infection	34 (5.1)	12 (3.4)	0.2104
Nasopharyngitis	14 (2.1)	3 (0.8)	0.1984
Investigations	118 (17.7)	76 (21.2)	0.181
Platelet count increased	30 (4.5)	17 (4.7)	0.8761
Blood glucose decreased	27 (4.0)	15 (4.2)	1
Aspartate aminotransferase increased	26 (3.9)	16 (4.5)	0.7413
Electrocardiogram QT prolonged	21 (3.1)	29 (8.1)	0.0007
Blood albumin decreased	17 (2.5)	14 (3.9)	0.2523
Alanine aminotransferase increased	15 (2.2)	6 (1.7)	0.6475
Blood potassium increased	15 (2.2)	4 (1.1)	0.2335

Haemoglobin decreased	14 (2.1)	6 (1.7)	0.8138
Respiratory, thoracic and mediastinal disorders	64 (9.6)	29 (8.1)	0.494
Cough	51 (7.6)	24 (6.7)	0.617

In the overall population treated with granules for oral suspension (n=667) no remarkable differences have been observed regarding safety. Note that for both AST and ALT in the overall paediatric population treated with granules observed frequencies are similar.

The SOH only provided a weight analysis on data from SP-C-013-11 study. The number of exposed children between 5-<8 kg is very low (n=4). No comparison can be made and no conclusion can be drawn for this critical weight category with the provided data.

Patients with at least one adverse event is higher in the weigh category 8-<15kg than in 15-<20kg in PA arm in SP-C-013-11: 114/186=61.3% versus 65/186=34.9% for episode 1; 35/61=57.4% versus 20/61=32.8% for episode 2.

Table 2 shows that the most frequently reported AEs by PT and episode was bronchitis; Episode 1: bronchitis, 67 patients (17.8%) in the PA arm and 47 patients (20.2%) in the AL arm; Episode 2: bronchitis, 24 patients (19.4%) in the PA arm and 20 patients (23.8 %) in the AL arm

Table 2: Incidence of Adverse Events Reported by at least 2% of Patients in any Treatment Arm by Primary System Organ Class and Preferred Term – SP-C-013-11 Sub-study (granules).

Treatment episode 1	PA	AL
Primary system organ class	n (%)	n (%)
Preferred term		
Patients dosed	376 (100.0)	233 (100.0)
At least one adverse event	183 (48.7)	122 (52.4)
Blood and lymphatic system disorders	32 (8.5)	30 (12.9)
Neutropenia	13 (3.5)	11 (4.7)
Anaemia	6 (1.6)	6 (2.6)
Gastrointestinal disorders	46 (12.2)	14 (6)
Abdominal pain	9 (2.4)	1 (0.4)
Vomiting	28 (7.4)	5 (2.1)
Infections and infestations	105 (27.9)	68 (29.2)
Bronchitis	67 (17.8)	47 (20.2)
Rhinitis	31 (8.2)	24 (10.3)
Investigations	42 (11.2)	40 (17.2)
Electrocardiogram QT prolonged	21 (5.6)	29 (12.4)
Alanine aminotransferase increased	9 (2.4)	5 (2.1)
Aspartate aminotransferase increased	11 (2.9)	9 (3.9)
Respiratory, thoracic and mediastinal disorders		

Treatment episode 1	PA	AL
Primary system organ class	n (%)	n (%)
Preferred term		
Cough	9 (2.4)	6 (2.6)
Treatment episode 2		
Patients dosed	124	84
At least one adverse event	56 (45.2)	34 (40.5)
Blood and lymphatic system disorders	10 (8.1)	12 (14.3)
Neutropenia	4 (3.2)	3 (3.6)
Monocytosis	3 (2.4)	6 (7.1)
Infections and infestations	32 (25.8)	23 (27.4)
Bronchitis	24 (19.4)	20 (23.8)
Rhinitis	18 (14.5)	5 (6.0)
Investigations	11 (8.9)	9 (10.7)
Electrocardiogram QT prolonged	3 (2.4)	5 (6.0)
Aspartate aminotransferase increased	5 (4.0)	1 (1.2)
Respiratory, thoracic and mediastinal disorders	4 (3.2)	0
Cough	4 (3.2)	0

Adverse events reported after treatment of one malaria episode within the paediatric population of sub study SP-C-013-11 is similar to the adverse event rates observed within the paediatric study SP-C-007-07.

Of note, in SP-C-13-11, if differences are compared between the 2 arms for each weight category, a higher incidence has been observed in PA arm compared to AL arm for notably the following PT: vomiting, transaminase increased, thrombocytopenia, conjunctivitis, cough, skin disorders, metabolism and nutrition disorder and hypercreatininaemia.

Vomiting is observed with a statistically higher incidence in PA arm compared to AL arm in pooled data (ISS granules), and notably in episode 1 of SP-C-013-11 study, whatever weight categories. The number of patients who vomited in the first 30 minutes is higher after PA granules administration than AL administration. There was however a lesser percentage of withdrawal due to vomiting in PA arm in children weighing < 20kg, compared to AL arm (1.7% vs 2.4% respectively) and vomiting did not appear related to palatability of the suspension.

Serious adverse event/deaths/other significant events

There were two unrelated deaths in the SP-C-013-11 sub-study; in the PA arm multi-organ failure following a road traffic accident and in the AL arm HIV infection. AE leading to death was in a patient who received PA granules and was reported during episode 1 (0.3%) (multi-organ failure following a road traffic accident) which was considered unrelated to the study drug.

For the Granules ISS population (is the overall population of patients <20 kg BW treated with granules for oral solution), no significant differences between the groups with regards to SAEs.

Laboratory findings

Adverse Events of Special Interest: *hepatotoxicity*

In the longitudinal (SP-C-013-11) repeat dose tablet sub-study, for episode 1, the incidence of any post dose rise in ALT $>3 \times \text{ULN}$ was 2.3% and $> 5 \times \text{ULN}$ was 1.3% respectively. This compares in the Phase II/III programme with any post dose rise in ALT $>3 \times \text{ULN}$ of 3.3% and $> 5 \times \text{ULN}$ of 1.4% (see table 2.7.4-44 in the clinical safety summary).

Comparing the incidence of any post dose rise in ALT $>3 \times \text{ULN}$ for the tablets to the granules within the longitudinal study (SP-C-013-11) - after treatment for episode 1 - shows that ALT $>3 \times \text{ULN}$ was 1.4% and $> 5 \times \text{ULN}$ was 0.8% ($>5 \times \text{ULN}$: 0%; **$>10 \times \text{ULN}$: 0.8%**) respectively. In the tablet group this was ALT $>3 \times \text{ULN}$ was 2.9% and $> 5 \times \text{ULN}$ was 1.6%. The incidence of ALT rising is comparable between patients $<20 \text{ kg}$ (granules) and $\geq 20 \text{ kg}$ (tablets); however in the paediatric patients 3 patients had **ALT levels $>10 \times \text{ULN}$** .

When paediatric patients (granule treatment) were treated for a second malaria episode no rise in ALT $>3 \times \text{ULN}$ was reported whilst for patients $\geq 20 \text{ kg}$ weight (tablet treatment) this was 1.6%.

Patients weighing $<8 \text{ kg}$ were few in numbers. Among the 7 patients with weight $<8 \text{ kg}$, no transaminase rise were observed; no firm conclusions can be reached in view of the scarce numbers.

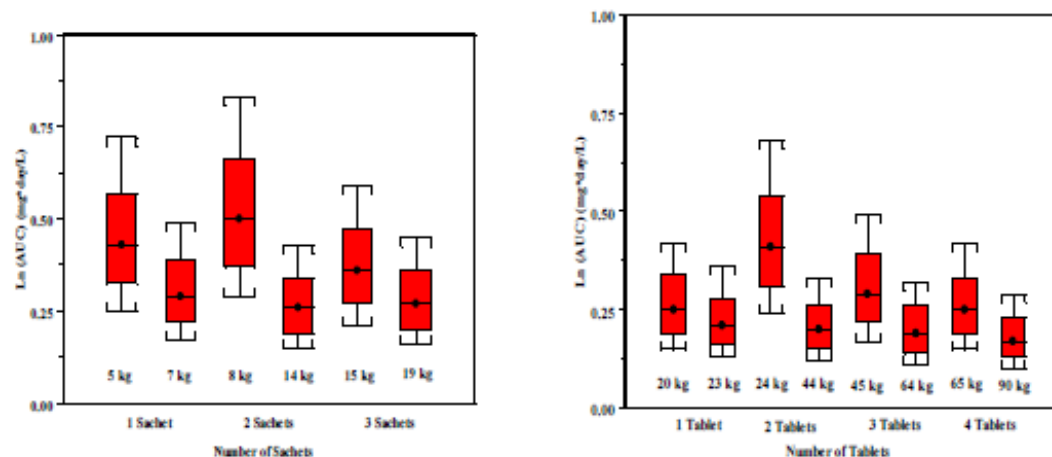
Based on provided data, no signal of incidence of hepatotoxicity emerged in children within 60 days of re-administration in the SP-C-013-11 sub-study report.

Table 17: Summary table of relevant results regarding highest value of ALT in different populations:

	Safety population ISS granules (SP-C-013-11 and SPC-007-07)		Safety population of SP-C-013-11 paediatric sub-study	
	8- $<15 \text{ kg}$	15- $<20 \text{ kg}$	$<20 \text{ kg}$	$>20 \text{ kg}$
ALT >1.5 - $\leq 3 \times \text{ULN}$	10/306 (3.3)	9/337 (2.7)	11/363 (3.0)	35/617 (5.7)
ALT >3 - $\leq 5 \times \text{ULN}$	3/306 (1.0)	1/337 (0.3)	2/363 (0.6)	8/617 (1.3)
ALT >5 - $\leq 10 \times \text{ULN}$	1/306 (0.3)	0/337 (0)	0/363 (0)	10/617 (1.6)
ALT $>10 \times \text{ULN}$	4/306 (1.3)	0/337 (0)	3/363 (0.8)	0/617 (0)

If percentages are compared by transaminase rise category of ISS granules population to patients $>20 \text{ kg}$ in SP-C-013-11, higher percentage ($4/306=1.3\%$) is observed in the 8- $<15 \text{ kg}$ group for ALT $>10 \times \text{ULN}$.

From the data shown, it is suggested that patients weighting 8- $<15 \text{ kg}$ could be potentially more at risk to high rise of transaminase $>10 \times \text{ULN}$ than patients weighting 15- $<20 \text{ kg}$. This would be based on higher pyronaridine exposure in this younger age group. Indeed, submitted data on pyronaridine exposure in patients stratified by body weight categories, suggests that pyronaridine concentrations in the youngest paediatric patients infected with malaria is higher compared to malaria infected children $>20 \text{ kg}$ and adults (figure below).



Box-plot depicting number of sachets and $\text{Ln}(\text{AUC})$ distribution of pyronaridine based on 3 dosing regimens for paediatric malaria patients (left) and Box-plot depicting number of tablets and $\text{Ln}(\text{AUC})$ distribution of pyronaridine based on 4 dosing regimens for adult malaria patients; bars represent 25th and 75th percentiles; whiskers represent 10th and 90th percentiles.

Hy's law

In SP-C-013-11 granules subgroup of the sub-study, hepatotoxicity events for the granules sub-study were defined as ALT >5 x ULN or Hy's law [ALT or AST >3 x ULN and total bilirubin >2 x ULN] at any post-dose time point. There was one case of Hy's Law in the PA arm during episode 1 on Day 7 and one in the AL arm on Day 28 of episode 1. The case in the PA arm was reported as an SAE (drug-induced liver injury) and occurred in a 2-year old patient 22-0173-P.

Since the sub-study was analysed one further serious adverse event of Hy's law has been reported in the third episode of dosing. This occurred in patient 21-0608-L, a 2 year old female who had no liver test rises in episodes 1 and 2 but developed a rise on episode 3 starting at Day 3 and fulfilling Hy's law criteria at Day 7. The patient had experienced abdominal pain fever on Day 0 of this episode but these cleared then moderate intensity abdominal pain reappeared with moderate painless hepatomegaly and on the basis of this, digestive parasitosis was suspected and albendazole was started (Day 6).

The DSMB considered that the liver abnormalities described for case 21-0608 fulfil criteria for Hy's Law. The exposure to albendazole and possibility of EBV infection were noted, but the DSMB agreed that the liver toxicity was probably due to Pyramax. It was noted that this was the first occurrence of a Hy's Law case during re-exposure to Pyramax and did not provide sufficient evidence of a specific risk of liver toxicity as a direct consequence of re-exposure; however, the pattern of maximum rise by Day 7 and subsequent fall immediately after followed the same pattern as the case that occurred on first exposure.

The two paediatric patients considered Hy's law cases were 2 and 3 years of age. Data from the popPK studies showed that the AUC of PA is higher in the lowest weight categories. As previously discussed, pharmacokinetic data may suggest that the observed hepatotoxicity in these young patients could be attributed to the apparent higher exposure to PA. It could however not be ruled out that hepatic immaturity might play a role. Also, it has been recognized that co-morbidity may pose a potential for increased hepatotoxicity (e.g malnutrition may predispose, through a lack of glutathione, to an increased risk of hepatotoxicity with Pyramax).

Based on the total of information obtained from the overall database, the cumulative number of Hy's Law is 6 out of the approx. 4000 patients exposed to pyronaridine-artesunate, i.e. 4 confirmed cases of Hy's

law without described confounding factors (including 2 cases with eosinophils rise), 1 confirmed case of Hy's law with confounding factor and 1 possible Hy's law case.

The following table summarizes the cases reported to date (also including non DSMB confirmed)

Table 18: Case summaries for patients fulfilling Hy's law (suspect and confirmed)

Patient ID and exposure	Age, Sex, Weigh	Hy's law attribution and summary of hepatic AE	complementary information	Outcome
09-2995:S-T First exposure (PA 540 :180 mg during 3 days in SP-C-005-06)	39 yo, F, 59kg	Hy's law confirmed by DSMB <u>D3 and D7 :</u> ALT 13xULN Tbili 3.3xULN AP Normal	D3: diarrhea treated with activated attapulgit during 2 days Unknown date : Eosinophils increase from 0 to 6% (compatible with allergic reaction? no information regarding any parasitosis) No other likely cause of liver toxicity identified	LFT's normal by Day 28
09-3037:O-S First exposure (PA 360:120mg during 3 days in SP-C-005-06)	14 yo, M, 39kg	Hy's law confirmed by DSMB <u>D3:</u> ALT 6.2xULN Tbili 3.0xULN AP Normal	D2: diarrhea treated with acitivated attapulgit D3: vomiting treated by Vogalene (unlikely cause of liver injury) Eosinophils rise from 0.1 to 17% on D3	LFT's normal by Day 7
05-1607:N-K First exposure (granules during 3 days in SP-C-007-07)	3 yo, F, 11kg	Hy's law confirmed by DSMB At baseline: mild/moderate ALT, AP and bilirubin elevation <u>D7 :</u> ALT 15xULN Tbili 2.4xULN AP 1.4xULN Jaundice to confirm because in the DSMB opinion but not in the provided narrative	D3 exposed to traditional medicine (contributory is unknown)	on D14 ALT improvement but abnormal but on D28 normalisation; Tbili not repeated
22-0173-P First exposure (granules during 3 days in SP-C-013-11)	2 yo, F, 10,2kg	Hy's law confirmed by DSMB <u>D7 :</u> ALT 24xULN Tbili 2.1xULN AP 1.8xULN ALT/ALP=13	Exposed to paracetamol (D5 and D10) and metamizole (D5, after the first increase of ALT on day 3)	Tbili normal by D14; ALT normal D28 Of note, reexposure to PA (protocol deviation) 118 days after: modest isolated increase of transaminases 1.3 N on D3

21-0608-L Third exposure (granules during 3 days in SPC-013-11)	3 yo, F, 9.5kg	Hy's law confirmed by DSMB <u>D7:</u> ALT 13xULN AST 20xULN Tbili 3.2xULN AP normal painless moderate hepatomegaly (factor of confusion: suspected parasitosis, positive EBV and use of albendazole)	Of note, no AE during first and second exposure (respectively 9 months ago and 2 months and half ago). Exposed to paracetamol (D1) Possibility of digestive parasitosis treated by albendazole on D7 for 3 days	LFT's normal D28
01-0050-P first exposure (tablets during 3 days in SPC-013-11)	31, F unknown	Hy's law could not be excluded ALP not available. No DSMB review <u>D7</u> ALT 9xULN AST 4.7xULN Bilirubin 2.7xULN	No rise of eosinophils No other ADR	LFT's normal D28
06-10777 (SPC-004-06)	26 yo, M unknown	Hy's law not considered by DSMB because it would have expected to see much higher ALT (3.4N on D7) associated with hepatocellular injury sufficient to be cause of bilitubin elevation (3.2N). Of note AP normal.		
B005 (SP-C002-05)	20 yo, F 46kg	Hy's law not considered by DSMB because of raised AP (cholestatic disorder)		
07-10329 (SP-C-004-06)	25 yo, M, unknown	Hy's law not considered by DSMB because of raised AP (cholestatic disorder)		

The fact that among the 6 cumulative confirmed Hy's law cases, 3 of them occurred in 2-3 year old children weighing around 10kg (9.5kg for 21-0608-L, 10.2kg for 22-0173-P case and 11kg for 05-1607 case), with one case with confounding factors (suspected parasitosis, positive EBV and use of albendazole) but two cases without confounding factors, is highlighted.

Adverse Events of Special Interest: QT prolongation

In the Granules subgroup of the sub-study, the number of patients with signal QTc values or signal QTc increase from Day 0 of actual episode, by episode and time between treatment episodes, (central ECG review) was submitted. Despite changes of >30 msec from Day 0, a low number of patients in the PA arm had a QTc of >450 msec and no patients with a QTc of >480 msec, with the exception of 1 case during episode 2 (QTcB, but not QTcF).

No patient in the PA arm had a QTcF of >450 msec. Larger increases from Day 0 to Day 2 were observed in mean PR interval, RR interval, QT interval, and QTcF in the AL arm than in the PA arm for most episodes. Changes of >30 msec from Day 0 were observed in a minority of patients in both the PA arm (up to 12%) and AL arm (up to 24%), but the proportion was slightly higher in the AL arm. This difference showed a p-value <0.05 during the first episode using Fisher's exact test. QTc of >450 msec were observed in a lower proportion of patients in the PA arm than in the AL arm. This difference showed a p-value <0.05 during the first episode using Fisher's exact test as well and was true for both the Bazett

and Fridericia corrections. No patients with a QTc of >480 msec were observed in the PA arm but 2 patients in the AL arm had a QTc > 480 msec during episode 2.

The higher incidence of QT prolongation in AL arm compared to PA arm should however be cautiously interpreted in view of questionable collection methodology.

Discontinuation due to adverse events

Table 3 and 20 show reasons for discontinuation in the overall patient population treated with granules and the patients in the substudy of SP-C-013-11.

Table 3: Subject Disposition – Granules ISS Population

	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Total n (%)
Patients treated (at least one dose)	667 (100.0)	358 (100.0)	1025 (100.0)
Patients who completed study	590 (88.5)	328 (91.6)	918 (89.6)
Patients who discontinued prematurely	77 (11.5)	30 (8.4)	107 (10.4)
Reason for withdrawal			
Adverse Event/Serious Ae	8 (1.2)	3 (0.8)	11 (1.1)
Consent Withdrawn	4 (0.6)	4 (1.1)	8 (0.8)
Death	1 (0.1)	0 (0.0)	1 (0.1)
Other	55 (8.2)	23 (6.4)	78 (7.6)
Patient Lost To Follow-Up	4 (0.6)	0 (0.0)	4 (0.4)
Protocol Violation/Non Compliance	1 (0.1)	0 (0.0)	1 (0.1)
Reason Not Databased	4 (0.6)	0 (0.0)	4 (0.4)

Table 20: Subject Disposition – SP-C-013-11 sub-study (granules)

	Pyronaridine artesunate n (%)	Artemether lumefantrine n (%)	Total n (%)
Patients randomised (all patients)	1015 (100.0)	671 (100.0)	1686 (100.0)
Patients treated (at least one dose with granules formulation)			
1 episode	376 (100.0)	233 (100.0)	609 (100.0)
2 episodes	124 (33)	84 (36)	208 (34)
3 episodes	35 (9)	20 (9)	54 (9)
4 episodes	28 (2.8)	20 (3.0)	48 (2.8)
5 episodes	2 (0.5)	0 (0)	2 (0.3)
Patients who completed study	0 (0.0)	0 (0.0)	0 (0.0)
Patients continuing in study at time point of sub-study analysis	367 (97.6)	229 (98.3)	596 (97.9)
Withdrawn from study prematurely	9 (2.4)	4 (1.7)	13 (2.1)
During active treatment period	3 (1.8)	1 (0.49)	4 (0.7)
During post-treatment follow-up	6 (2.6)	3 (1.3)	9 (1.5)
Other time point	0 (0.0)	0 (00)	0 (00)
Reason for withdrawal			
Treatment failure	0 (0.0)	0 (0.0)	
Adverse event	1 (0.3)	0 (0.0)	
Death	1 (0.3)	0 (0.0)	
Protocol violation	2 (0.5)	0 (0.0)	
Lost to follow-up	0 (0.0)	0 (0.0)	
Withdrawal of consent	2 (0.5)	3 (1.3)	
Pregnancy	0 (0.0)	0 (0.0)	
Study terminated by Sponsor	0 (0.0)	0 (0.0)	
Other	1 (0.5)	1 (0.4)	

The overall incidence of treatment-emergent AEs leading to study drug discontinuation or withdrawal from the study was low and similar in each group.

2.6.1. Discussion on clinical safety

The SOH submitted safety data for paediatric patients (aged 0 to 11 years of age; <20kg BW) treated with granules for oral suspension (sub study SP-C-013011; PA =376 patients; AL = 233 patients). Integrated safety data from all paediatric patients <20 kg of BW (n=667) was submitted as well. In study SP-C-013-11, a higher frequency in vomiting during treatment episode one was observed. It was however clarified that this was not attributed to palatability of the suspension and thus without impact on treatment compliance. Other reported adverse events are similar in frequency in both the PA as the AL arm.

Hepatotoxicity has been a major point of concern for Pyramax. Since data show that in paediatric patients there is a trend towards higher exposure to pyronaridine, it cannot be ruled out that this has its effect on

hepatotoxicity. In the current application, Hy's law cases (from study SP-C-013-11) were reported in very young children (2-4 years of age; bodyweight approximately 10 kg or lower). The narratives of these patients suggest that either concomitant medication or an underlying disease may be associated with an increase in values of hepatic enzymes /bilirubin. In view of the observed toxicity and exposure, it was questioned if the safe use of Pyramax (granules for oral suspension) in these small children is justified, also taking account of the fact that in the study, subjects with comorbidities, such as HIV, HCV and malnutrition were excluded.

Other safety findings

Although there seems no clear evidence for an increased safety risk with PA re-dosing based on ECG findings, a dedicated QT/QTc study according to ICH E14 guideline, should be considered by the SOH. A cautionary statement is appearing in SmPC, section 4.4, regarding its use in at risk patients, ie. those with congenital prolongation of QTc interval, hypokalaemia, dehydration, cardiac arrhythmia, heart failure, treated concomitantly with other drugs that can block potassium channels, and those recently treated with medicinal products with long elimination half-life and known to prolong the QTc interval that may still be circulating at the time Pyramax treatment course is commenced.

Additional expert consultation

To further clarify the appropriate use of Pyramax granules in the young population, an expert meeting was convened. Based on the current data (as derived from clinical data in children ≥ 5 kg to adults), it was questioned what level of reassurance in terms of hepatotoxicity had been gained. It was also questioned to what extent the data accumulated are compatible with the use of the drug in asymptomatic patients without systemic liver testing (i.e. while patients in the study could only be treated if ALT<2ULN) and if extrapolation beyond the study population would be possible. Experts asserted that there is indeed sufficient evidence to use the medicinal product in the proposed way- i.e. in asymptomatic patients without systematic liver testing-, also considering a broader population (e.g. co-infection, having experienced transaminase rise more than 5ULN or Hy's law after the initial or previous treatment) provided that an effective RMP be put in place, including appropriate pharmacovigilance measures and the commitment of a phase IV study to be carried out. The experts were also unanimous in their view that routine liver function testing would not be possible in the intended clinical setting. Also, in view of the short treatment duration, no stopping rules can be formulated for emerging signs /symptoms of liver injury (since the course would have stopped already in anyway). This contrasts though to treatment emerging anaphylaxis (requiring immediate cessation of therapy). Also, as stated in the Product literature, treatment should not be started in those with known underlying hepatic injury. Thus, retreatment in the affected community would therefore be permitted unless the patient had history of anaphylaxis, clinical jaundice or otherwise known severe liver disease (decompensated cirrhosis, Child-Pugh stage 3 or 4).

With reference to the proposed study, it should contain the following elements:

- a. Population: All those with malaria requiring oral therapy to be included:
 - all age groups to be represented (from 5kg body weight onwards)
 - co-infection: HIV infected and those suffering chronic hepatitis (B, C). Also, in view of high prevalence of hepatitis E in Africa and its unsure role in causing chronic liver disease in those co-infected with HIV, serological screening for hepatitis E should be included in the protocol.
 - liver function tests: patients with abnormal liver function tests allowed, but with exclusion of those presenting with decompensated cirrhosis

- b. Repeat use: to be included
- c. Drug-drug interaction: should be investigated for all cases in which DDI has a potential; particular focus to be placed on interaction with P450 cytochrome enzymes and potential mitochondrial toxicity.
- d. Nutritional status: to be examined, with height/weight data to be collected for population < 20 kg
- e. Decision tool (as proposed)
- f. Testing: standard biochemical panels to be used, to determine whether clinical testing misses significant numbers with cirrhosis

2.6.2. Conclusions on the clinical safety

Overall, safe use of Pyramax Granules in paediatric patients – in particular the youngest- considered in a broader population (as compared to the restrictive conditions in study SP-C-013-11) and without systematic liver function testing is justified, provided an effective RMP be put in place, including appropriate pharmacovigilance measures and the commitment of a phase IV study to be carried out. To this purpose, the SOH's proposal for the phase IV study can be overall agreed (see further). Moreover, the SmPC reflects the limitations of the data in very young children and includes specific warnings (e.g. caution in case of malnutrition).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Product Information.

The CHMP considers the following measures necessary to address issues related to safety:

Post-opinion measure (s)	Motivation
Proposed post-opinion measure with proposed classification:	Post-registration study protocol to derive further reassurance on the use of PYRAMAX under enlarged conditions (retreatment, co-infections, no systematic liver testing, very small children [notably <1 year of age] with particular issues on malnutrition) Planned to start in January 2016

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed the attached PRAC Rapporteur assessment report.

The SOH submitted an updated RMP, version 12.1 following the PRAC meeting, to address comments in the rapporteur's assessment report and to align with appropriate guidance and template.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Neutropenia Vomiting Diarrhoea Interaction with drugs metabolised through CYP2D6 or via P-gp efflux
Important potential risks	Severe Malnutrition (impact on hepatotoxicity of pyronaridine in relation to GSH stock depletion) Use in pregnancy and lactation • Passage into breast milk • Embryotoxicity/teratogenicity Neurotoxicity Prolongation of QT and/or bradycardia Induction of resistance Tissue accumulation of pyronaridine with inflammation and degenerative changes Skin discolouration Drug interactions with TB or HIV agents metabolised via CYP2D6 pathways
Important missing information	Hepatotoxicity in patients with suspected cumulative risk factors: repeat course of PYRAMAX notably with short delay of re-introduction, malnutrition, co-infections (HBV, HCV, HIV), co-administration of drugs to be associated with mitochondrial toxicity (i.e. valproate, antiretroviral drugs), other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis), increased liver transaminases before administration, co-administration of paracetamol, use of herbal medicines. Safety in very young children (i.e. infants <10 kg notably 5-8 kg), including repeated dose Off-label use in infants under 5 kg in weight Safety in elderly patients HIV/AIDs infection Significant anaemia (Hb < 8 g/dL) Haemoglobinopathies (e.g. thalassaemia, sickle cell and G6PD deficiency) Patients with hepatic, renal, or cardiac impairment

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
SP-C-013-11 (WANECAM) A Phase IIIb/IV comparative, randomised, multi-centre, open label parallel 3-arm clinical study to assess the safety and efficacy of repeated	To compare the efficacy and the safety of repeated ACT therapy over a period of 2 years (PA or DHA-piperaquine will be compared to either	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Neutropenia Prolongation of QT and/or bradycardia Induction of resistance	Recruitment complete and in follow up	Final CSR due 31 September 2016

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
administration of pyronaridine-artesunate, dihydroartemisinin-piperaquine or artemether-lumefantrine or artesunate-amodiaquine over a two-year period <u>in children and</u> adult patients with acute uncomplicated <i>Plasmodium</i> sp. malaria. Category 3	AS-AQ or AL) in children and adults	Safety in very young children (ie. infants <10 kg notably 5-<8 kg) in weight, including repeated dose Significant anaemia (patients with Hb < 8 g/dL)		
SP-PV-001-12 Pregnancy Registry Category 3	Monitor all pregnancies and their outcomes	Use in pregnant and lactating women – risk of embryotoxicity/teratogenicity	Ongoing	Annual updates Final report due 31 December 2015
SP-C-021-15 Phase IIb/IV Cohort Event Monitoring study to evaluate the safety in patients after the local registration of PYRAMAX Category 3	To assess the safety of Pyramax in patients to include those with underlying liver function abnormalities, co-morbid conditions, such as HIV, and also infants (<1 year of age)	Increases in liver transaminases (including rare Hy's Law cases) Exacerbation of anaemia Interaction with metabolised through CYP2D6 or via P-gp efflux Severe Malnutrition (impact on hepatotoxicity of pyronaridine in relation to GSH stock depletion) Hepatotoxicity in patients with suspected cumulative risk factors: repeat course of PYRAMAX notably with short delay of re-introduction, malnutrition, co-infections (HBV, HCV, HIV), co-administration of drugs to be associated with mitochondrial toxicity (i.e valproate, antiretroviral drugs), other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis), increased liver transaminases before administration, co-administration of paracetamol, use of herbal medicines Safety in very young children (i.e. infants <10 kg notably 5-8 kg), including repeated dose Safety in elderly patients HIV/AIDs infection Significant anaemia (Hb < 8 g/dL)	expected to start by 30 January 2016	Final CSR due 30 September 2018

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports
SP-C-018-13 Study: Randomized, open-label trial of the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetrphosphate-artesunate or dihydroartemisinin-piperaquine phosphate for radical cure of acute Plasmodium vivax malaria in soldiers Category 4	Evaluate the safety, tolerability and efficacy of primaquine against relapse when combined with pyronaridine tetrphosphate-artesunate or dihydroartemisinin-piperaquine phosphate for radical cure of acute Plasmodium vivax malaria in soldiers in Indonesia	<i>Plasmodium vivax malaria</i> in adults	Recruitment complete and in follow up	Final CSR due 31 December 2015
SP-C-019-14 Study: Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria Category 4	Monitor efficacy and safety in adults treated with tablets in Cambodia	Induction of resistance	Ongoing	Final CSR due 31 December 2015
SP-C-020-15 Study: Pyronaridine-artesunate and artemether-lumefantrine for the treatment of paediatric uncomplicated <i>falciparum</i> malaria in Western Kenya Category 4	To assess the safety and efficacy of the paediatric formulation of Pyramax compared to that of Artemether-Lumefantrine	Significant anaemia (Hb < 8 g/dL)	Recruiting	Final CSR due 31 December 2017

Risk minimisation measures

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Increases in liver transaminases(including Hy's Law cases)	Information in sections 4.2, 4.3, 4.4, 4.8, 5.3 of the SmPC related to <u>hepatic restriction conditions and precautions recommendations</u> . Also in Section 4.8, advice on the effect of Pyramax on transaminases in Caucasians will be amended.	None.
Exacerbation of anaemia	Information in sections 4.4 and 4.8 of the SmPC	None
Neutropenia	Information in section 4.2 and 4.4 of the SmPC	None

Vomiting	Information in sections 4.4 and 4.8 of the SmPC	None
Diarrhoea	Information in sections 4.4 and 4.8 of the SmPC	
Interaction with medication metabolised through CYP2D6 or via P-gp efflux	Information in sections 4.5 and 5.2 of the SmPC	None
Important Potential Risks		
Severe Malnutrition	Information in sections 4.4 and 5.1 of the SmPC	None
Use in pregnant and lactating women	Information in sections 4.4, 4.6 and 5.3 of the SmPC	None
Neurotoxicity	Information in section 5.3 of the SmPC	None
Prolongation of QT and/or bradycardia	Information in Section 4.4 and 4.8 of the SmPC	None
Induction of resistance	Information in section 5.1 of the SmPC	None
Tissue accumulation of pyronaridine with inflammation and degenerative changes	Information in section 5.3 of the SmPC	None
Skin discolouration	Information in section 5.3 of the SmPC	None
Drug interactions with TB or HIV agents metabolised via CYP2D6 pathways	Information in sections 4.5 and 5.2 of the SmPC	None
Missing Information		
Hepatotoxicity in patients with suspected cumulative risk factors	Warnings about the lack of information on repeat dosing are provided in sections 4.4 of the SmPC	None
Safety in very young children (ie. infants <10 kg notably 5-8 kg) including repeated dose	Information in section 4.2, 5.3 of the SmPC	None
Off label use in infants under 5 kg in weight	Information in section 4.1, 4.2, 5.1 of the SmPC	None
Safety in elderly patients	Section 4.2 indicates the lack of information and caution in these patients	
HIV/AIDs infection	Section 4.4 indicates the lack of information and caution in these patients	None
Significant anaemia (patients with Hb < 8 g/dL)	Information in section 4.4 and 4.8 of the SmPC	None
Haemoglobinopathies	None	None
Patients with hepatic, renal, or cardiac impairment	Information in Sections 4.2 and 4.3 of the SmPC regarding hepatic impairment Caution with regard to moderate renal impairment is provided in Section 4.2, 4.4 and 5.2. No special precautions are considered to be required for cardiac impairment	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the summary of the pharmacovigilance system submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy Pyramax in the treatment of uncomplicated malaria due to *P.falciparum* and *P.vivax* has been demonstrated in two pivotal studies (SP-C-004-06 and SP-C-005-06) in patients weighing more than 20 kg with the tablet formulation.

Regarding the granule formulation subject to this extension application, the tablet and the granule formulation are not considered bioequivalent as study SP-C-017-12 demonstrated that the PK profile for the artesunate component is different, i.e. the C_{max} is 45% lower with the granule formulation (For pyronaridine, bioequivalence has been demonstrated). However, efficacy with the granule formulation in children between 5 and 20 kg has been demonstrated in the longitudinal interim paediatric sub-study SP-C-13-11 and SP-C-007-07:

- Although descriptive, the data from sub-study SP-C-13-11 in which PYRAMAX is compared with AL in around 600 children with bodyweights ranging from 8 to 20 kg (n=372 with PYRAMAX and n=232 with AL), provide reassurance regarding the efficacy of PYRAMAX as compared to AL (with results even favoring PA: Day28/Day42 corrected ACPR-EE 100%/99.3% vs 98.4%/97.8%) in children weighing less than 20 kg. The efficacy is comparable in adolescents and adult ≥20 Kg. Although the data were very limited in children below 10 kg, these data are suggestive of comparable efficacy with AL.
- As regards the issue of retreatment as part of the claimed labelling on this line extension (and subject to parallel a type II variation for the tablet formulation in adults and children >20 kg), the efficacy has been substantiated through the overall amount of data provided by study SP-C-013-11 in children above 20 kg and adults, with no particular signal towards a downgraded level of efficacy over time. In the subgroup of children concerned by the line extension of the granule formulation, some reassurance has been gained on the efficacy of retreatment, with 124 children from 5 to 20 kg being retreated once including 59 children from 8-15 kg and 56 children from 15-20 kg, data are more limited for episodes >2 (around 30 children in episode 3). Among the 52 children <10 kg, there were retreatment data on 10 children (one child treated 4 times, 3 children treated 3 times, 6 treated 2 times). In this very young population, the short median delay of retreatment (39.5 days) particularly illustrates the medical need.

Uncertainty in the knowledge about the beneficial effects

There is only limited data on efficacy in children weighing less than 10 kg. Therefore, the adequacy of the dose in very young children (<10 kg) is expected to be further substantiated by ongoing/planned clinical studies.

There are some uncertainties regarding the acceptability of the granule formulation in young children, although no immediate issues were identified in clinical trials. Ongoing and planned clinical studies will provide further information regarding the acceptability of the drug product in this population.

Risks

Unfavourable effects

The most important identified risk with Pyramax concerns the hepatotoxicity. Mechanistic studies show this to be dependent on the intracellular glutathione level or the glutathione redox cycle and may be caused by oxidative damage. The suggested potential dose-dependent hepatotoxicity of pyronaridine could be linked, as paracetamol, to the formation of a hepatotoxic reactive metabolite which could be

detoxified by glutathione (GSH). In the setting of a depletion of glutathione, inhibition of mitochondrial respiration occurs, causing cytolytic hepatitis.

To date, among a total of 4200 patients exposed to pyronaridine-artesunate, there have been a limited number (n=6) of reported Hy's law cases of which 4 confirmed cases without confounding factors. Mostly cases were asymptomatic and all resolved.

Uncertainty in the knowledge about the unfavourable effects

The cumulative safety data available so far provided sufficient re-assurance to use Pyramax in asymptomatic patients (including children from 5 kg) without any systematic liver testing.

There are limited data in children <10 kg (n=52), including only 7 children weighing <8 kg and 14 children between 8-9 kg. Only 10 children were retreated once. There is no clear signal that the safety in very young children (< 10kg) would differ from older children. Moreover, exclusion criteria in clinical trials result in limited information on the safety of Pyramax in children with concomitant conditions such as co-infections or malnourishment. In the light of the proposed mechanism of hepatotoxicity, malnourishment is considered a potential risk factor for hepatotoxicity of pyronaridine through depletion of the GSH stock. Further studies should inform the safety profile in these children as in children <10 kg. As such, a post-marketing study has been planned to derive further reassurance on Pyramax safety in a broadened population, i.e. to include patients with co-infections and in which systematic liver testing is not routinely performed. This study will be conducted in both adults and children, and will plan to include a significant number of children <1 year of age and will explore the impact on malnutrition.

Benefit-risk balance

Importance of favourable and unfavourable effects

Benefit-risk balance

The cumulative safety data available so far provided sufficient re-assurance to use Pyramax in asymptomatic patients (including children from 5 kg) without any systematic liver testing.

Discussion on the benefit-risk balance

Despite existing uncertainties on the efficacy and safety in very young children (<10 kg) the benefit/risk of Pyramax in children from 5 kg with a specific granule formulation can be considered positive. The limited data are reassuring that the efficacy and safety in children <10kg is not different to children >10kg.

This new formulation would provide an appropriate, safe and efficacious treatment option for the management of uncomplicated malaria in the main risk groups in endemic areas.

Remaining uncertainties surrounding the efficacy and safety of Pyramax in young children (<10 kg) will be further addressed in studies as detailed in the RMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Pyramax in the following indication is favourable:

Pyramax Granules for oral suspension are indicated in the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in children and infants weighing 5 kg to under 20 kg.

Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4).

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the Scientific Opinion

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Scientific Opinion Holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Scientific Opinion and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.